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THE USE OF SULFANILAMIDE IN THE TREATMENT OF ACUTE GLOMERULAR NEPHRITIS.

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It has been many years since Loehlein[9] in 1907 presented evidence to show that acute glomerular nephritis was the direct result of streptococcic infections. Since then the question has been the subject of much discussion, and though it is now generally recognized that infections by hemolytic streptococci precede with great frequency the onset of acute glomerular nephritis, the exact relationship between the two has never been accurately defined.[3–5,12a,c,13,19,22,24] Evidence, however, has been presented to show that a continuation of the infection or recurrent infections due to hemolytic streptococci predisposes to a progression of the nephritis and is the prime factor in preventing recovery or in leading to chronic nephritis.[12a,c,13,18,24]

The great regularity with which a marked increase in the antistreptolysin content of the blood serum occurs during the course of acute glomerular nephritis,[12b,14,17] even when cultures from the pharynx or other foci of infection fail to show hemolytic streptococci, is an additional argument in favor of the close association between this particular form of infection and acute hemorrhagic nephritis.

These facts do not, however, exclude the possibility that other bacteria, such as the *Streptococcus viridans*, the pneumococcus or the gonococcus may be concerned in the origin of some instances of acute nephritis. Indeed, there is reason to believe that they do so, though infections by these organisms are probably concerned with the origin of a comparatively small proportion of cases.

Since the persistence of infection may be of great importance in determining the course of the nephritis much emphasis, during the last few years, has been placed on the elimination of foci of infection. It has been necessary to rely largely upon such surgical measures as removal of tonsils and adenoids, or the drainage of infected paranasal sinuses to accomplish this. The efficacy of these surgical procedures has been questioned,[6,16] and has rarely been attended by brilliant results, for it has often been impossible by these means alone to cure completely the infection.

The great value of effecting complete cure of the acute nephritis lies in the fact that once the nephritis has healed, a recurrence rarely if ever occurs, even though the patient experiences one or more serious infections due to the hemolytic streptococcus.[8,12a,c] If, on the other hand, the disease persists, even in quiescent form, subsequent infections by hemolytic streptococci are liable to cause acute and sometimes serious exacerbations of the disease.[12a,c,13,18,24] Until the introduction of chemotherapy, therefore, the available treatment consisted principally in prolonged rest, diet, and surgical removal of the foci of infection. But with the demonstration of the highly effective action of sulfanilamide upon the hemolytic streptococcic infections, the possibility of using this chemical to combat infections associated with acute hemorrhagic nephritis naturally came to mind.[12d] A series of 42 cases of acute nephritis have therefore been treated, during the acute phase of the disease, with sulfanilamide. The effect upon the infection and the later course of the nephritis in these patients has been contrasted with 108 cases of acute nephritis which had not been treated with sulfanilamide.

The work was started at a time when sulfanilamide was the only chemical available for the treatment of infections caused by hemolytic streptococci. Its efficacy for this purpose had been amply demonstrated. The work of Marshall, Cutting and Emerson[15] had shown, moreover, that administration of large amounts of the drug exerted no harmful effect on the kidneys of dogs, and a vast number of subsequent observations in the human being have upheld these conclusions. It is, however, well recognized that sulfanilamide is not as rapidly excreted in the presence of even slight disease of the kidney as it is in the normal individual, and the drug is prone, therefore, to accumulate in comparatively high concentration in the blood even when the form of nephritis is mild. Since these studies were started three other drugs, namely sulfapyridine, sulfathiazole and sulfadiazine, have come into use. In spite of their efficacy, it

seemed highly undesirable to employ them for the treatment of any infection associated with nephritis, for both sulfapyridine and sulfathiazole are known to damage occasionally the kidneys either through the excretion of the acetylated form in crystals or by direct action upon the cells of the organ. Though sulfadiazine may be less likely to produce these injurious effects, experience has not been sufficiently extensive with this drug to warrant its use in patients suffering from nephritis.

In December, 1936, we began to use sulfanilamide in treating patients with acute glomerular nephritis. It has been employed almost exclusively in those patients from whom beta hemolytic streptococci have been cultured from some focus. We have treated only those patients who had a well-defined acute onset of their nephritis and only those who were admitted to the hospital within 2 months of this onset. In most instances they were admitted within a few days after the disease had manifested itself. We now have treated 42 such patients. The nephritis was regarded as mild in 11 cases (26%), moderately severe in 16 (38%), and severe in 15 (35%). Some of these patients exhibited marked albuminuria, hematuria, cylindruria, low renal function, azotemia, hypertension and edema. In 25 instances the nephritis followed acute tonsillitis, in 4 sinusitis, in 5 skin infections, in 1 scarlet fever, and in 2 puerperal infection. In some patients there was more than one focus. The interval from the prodromal infection to the onset of the nephritis averaged 13 days. The interval from the time the nephritis had manifested itself until sulfanilamide was administered varied in different cases from 1 to 173 days but averaged 26 days and in 27 cases was less than 14 days.

In order that we might evaluate the manner and extent to which the sulfanilamide therapy modified the course of acute hemorrhagic nephritis in these patients we have analyzed for control the records of 108 patients fulfilling all the requirements which we have presented above whom we have followed since 1925. We have selected at random 70 of this group and tabulated the course in great detail. This group has had essentially the same clinical and bacteriologic studies and the treatment has been similar in every way except that they did not receive sulfanilamide. The extent of the nephritis in 70 patients of this group was found to be mild in 17 cases (24% ±), moderate in 24 (34% ±), and severe in 29 (41% ±). Thus it may be seen that the severity of the disease in the treated and untreated groups is comparable. The interval from infection to the onset of nephritis was found to average 10.3 days as compared with 13 days in Group I. (Throughout this paper we shall refer to the control group as Group II and to the ones receiving sulfanilamide as Group I.)

The dosage which we have prescribed for our patients has varied from 1.2 to 6 gm. per day. The commonest dose, however, was a

total of 2.4 or 3.6 gm. divided into 6 equal doses at 4-hour intervals. The total amount of the drug given to any patient has varied from 6 to 169 gm. (average 49 gm.). The drug was administered over a period of 3 to 63 days (average 17 days). The blood concentration was followed in 32 patients and was found to vary from 4.5 to 18 mg. per 100 cc. In 13 subjects the level reached 10 mg. per 100 cc. at some time during the therapy. It was found that there was a greater variation, from day to day, of the blood concentration of the chemical than we have observed in subjects treated for other (non-renal) conditions. This has been attributed to the frequently changing renal function.

Since Southworth[20] found that acidosis may develop in association with sulfanilamide therapy we have usually given 0.6 gm. of sodium bicarbonate with each dose of the former. This has been used in spite of the fact that many of our patients have been edematous. No attempt was made to limit the fluids to any extent greater than was necessary to control the edema.

Toxic Reactions Due to Sulfanilamide. Mild toxic reactions characterized by headache, nausea, or vomiting developed in 3 patients. Seven patients developed fever and 2 a slight anemia. The drug was promptly discontinued in each of these instances and the symptoms rapidly abated. Occasionally difficulty was encountered in differentiating the symptoms of the nephritis from those of sulfanilamide intoxication. No serious complications were encountered.

Results of Therapy. Foci of Infection. In view of the great importance accorded to the acute infections which precede the development of nephritis it naturally was of interest to determine whether sulfanilamide had been effective in combating such infections. In our studies we have paid particular attention to the beta hemolytic streptococcus, as this organism is apparently the one of etiologic significance in by far the great majority of the cases. Table 1 and Figure 1 show the results of some of the throat cultures which have been made. It is quite noteworthy that whereas 71% of the patients in Group I had positive throat cultures just before sulfanilamide was begun, only 15% yielded positive cultures shortly after its discontinuance. This incidence is little more than is found in normal individuals in Baltimore in the winter months.[11]

It may be observed that, on admission, the throat cultures were positive for beta hemolytic streptococci in 76% of the patients in Group I and in 85% of the ones in Group II. Some subjects had several foci containing these organisms. They were obtained from the throats of all but 7 patients in Group I before sulfanilamide was started. In 2 of the 7 they were cultured from a skin infection, in 1 from an infected sinus and in 1 from the uterus. At the time of discharge from the hospital the infection in these subjects had cleared up and the number of patients giving positive throat cul-

tures was decidedly less, being 15% in Group I and 26% in Group II. It should be mentioned here that this change has been aided to a large extent by the performance of tonsillectomies in more than one-half the cases, by the drainage of infected sinuses in several instances, by the extraction of teeth with periapical abscesses, and by other similar procedures.

TABLE 1.—NUMBER OF PATIENTS FROM WHOM BETA HEMOLYTIC STREPTOCOCCI WERE RECOVERED ON THROAT CULTURE.

	No. +.	No. neg.	Total.	Positive, %.
On admission:				
Group I	29	9	38	76.3
Group II	58	10	68	85.0
Before sulfanilamide:				
Group I	27	11	38	71.0
After sulfanilamide:				
Group I	5	28	33	15.0
On discharge:				
Group I	5	27	32	15.6
Group II	15	42	57	26.3
Six months later:				
Group I	5	20	25	20.0
Group II	11	32	43	26.6

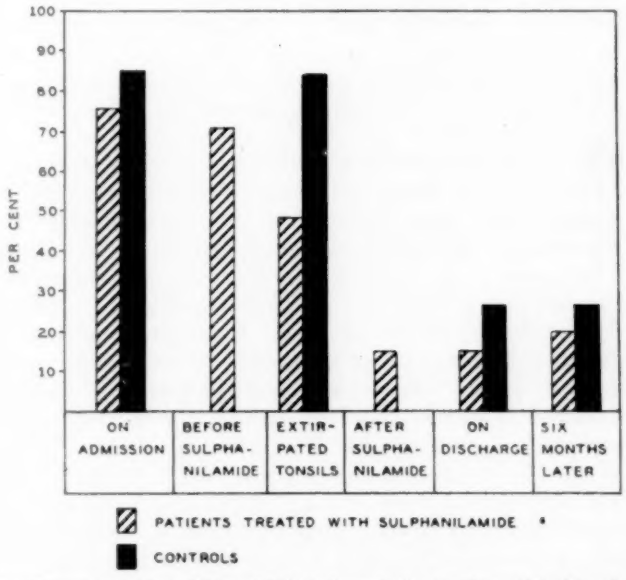

FIG. 1.—Percentage of patients with beta hemolytic streptococci in throat cultures.

We were permitted to repeat the throat cultures 6 months later on 25 subjects in Group I and on 43 subjects in Group II. Positive cultures were obtained in 20% of the former and 28% of the latter.

Of greater concern than the throat cultures was the incidence of organisms in the tonsils. The latter were removed from 38 patients

in Group II. The tonsils of 32 of these patients were macerated and cultured for beta hemolytic streptococci. The cultures were found to be positive in 27 subjects (84%). Tonsillectomy was performed on 29 patients in Group I. Cultures were made from 28 subjects, 13 (47%) of which yielded positive cultures. This incidence was found to be higher than we had at first anticipated, though it is considerably lower than that of the untreated patients. It is quite important to point out that sulfanilamide had not been administered, unfortunately, for at least a week preceding tonsillectomy, in 12 of the 28 subjects. Nevertheless, it is now known that the administration of relatively large doses over long periods of time may not render the tonsils sterile. We have regarded the persistence of these organisms as being responsible for some of the flare-ups which we have witnessed.

Colebrook and Purdie[2] have reported that hemolytic streptococci were recovered from cervical swabs taken on discharge from the hospital in 39 of 81 (48%) of their cases of puerperal infection that had recovered under sulfanilamide, and that 6 of 35 patients (17%) still showed positive cultures for hemolytic streptococci 3 to 6 weeks later. In experimental infections, Levaditi and Vaisman,[7] Long and Bliss,[10] and Colebrook and his associates[2] have reported the persistence of latent foci of hemolytic streptococci in mice treated over long periods with sulfanilamide. It is for these reasons that the various surgical methods have continued to be employed with equal vigor as in the past.

Changes in the Antistreptolysin Titer. Since 1930, we have made rather frequent determinations of the antistreptolysin titer of the serum. In Figure 2 the titers of antistreptolysin of both groups are recorded during the course of the disease. On admission the titer in Group I was found to vary from 50 to 500 units with an average of 198 and was over 100 in 27 of 31 subjects. The titer in Group II was within the same range, though not quite as high, varying from 16 to 500 with an average of 168, and being over 100 in 21 of 33 subjects. The average level in Group I, at the time sulfanilamide was started, was 223 units. On the completion of the treatment the average level was 239 units. At the time of discharge the titers were found to remain high in Group I, ranging from 50 to 500 units with an average of 199 and being over 100 in 27 of 30 subjects. In Group II it was found to vary from 16 to 1666 with an average of 222 and was over 100 in 21 of 33 patients.

Thus it may be stated that in spite of what antibacterial effect the sulfanilamide may have exerted upon the streptococcus, the immunologic reaction, as exhibited by the antistreptolysin titer, continued to develop in the usual manner. There was an actual increase in the titer during treatment with the drug. The titer was lower at discharge than on admission in 9 of 27 subjects (33%) in Group I, and in 11 of 32 subjects (34%) in Group II. It had in-

creased in 11 of 27 subjects (40%) in the former group and 15 of 32 (47%) in the latter.

The titer was again determined in some of the patients approximately 6 months later. With the improvement of the nephritis in most of the patients, and the recovery in some, there was found a marked decrease in the number of units in each group. In Group I the titer was found to vary from 25 to 333 units with an average of 131, and in 16 of 29 patients it was over 100. The results in Group II were found to show essentially the same decrease in the titer, but it is, indeed, worthy of mention that whereas in Group II, during the 6 months following discharge, there was a rise in titer in 5 of 23 subjects, in Group I there was a definite decrease in the titer in every patient.

Effect on the Kidneys. (*a*) *Changes in Urinary Findings.* On admission 99% of the subjects in each group had albuminuria. In most instances this was marked. Comparisons of the urinalyses before and after sulfanilamide therapy show that there was a very slight increase in the albuminuria in 2 cases. The remainder exhibited a marked decrease. This improvement continued in all but 1 patient after sulfanilamide was stopped. At the time of discharge there was a great reduction in the number of patients showing albuminuria. As shown in Figure 2, only 31% of the ones who had received sulfanilamide showed albuminuria as contrasted with 61% in Group II.

Table 2.—Changes in Urinary Findings.

	4+.	3+	2+.	+.	I.	0.	Total +.	Total.
				Albumin.				
On admission:								
Group I	8	9	9	7	4	1	37	38
Group II	25	15	14	9	6	1	69	70
On discharge:								
Group I	0	0	1	2	9	26	12	38
Group II	6	3	3	12	19	27	43	70
Six months later:								
Group I	0	1	2	6	5	19	14	33
Group II	2	4	2	9	19	19	24	45
				Formed Elements.				
On admission:								
Group I	24	6	6	0	2	0	38	38
Group II	38	9	14	8	1	0	70	70
On discharge:								
Group I	0	1	5	12	9	11	27	38
Group II	8	3	14	13	16	16	54	70
Six months later:								
Group I	1	2	4	4	3	19	12	33
Group II	2	6	7	7	11	22	33	55

Not only was there a reduction in the incidence, but also in the degree of albuminuria. In no patient in Group I was this greater at discharge than on admission. This did occur, however, to 1 patient in Group II. Urinalysis 6 months later showed a slight

increase in albuminuria in 6 of 33 patients (18%) in Group I, whereas of 55 subjects in Group II there was a slight increase in 17 (31%), moderate in 1 (1.8%) and marked in 2 (3.6%).

On admission, every patient in each group showed formed elements in the urine and usually in large quantities. Comparison of this finding before and after sulfanilamide therapy demonstrated a very slight increase in 1 subject, but a decrease, marked in most instances, in the others. The improvement continued, except in 3 patients, throughout the remainder of the stay in the hospital. However, the number of formed elements in the urine at the time of discharge was much less than on admission in all of the patients in Group I. In contrast, there were 5 (7%) in Group II who showed an increase, this being slight in 4 and moderate in 1. As may be seen in Figure 2, there was a fair number of patients in

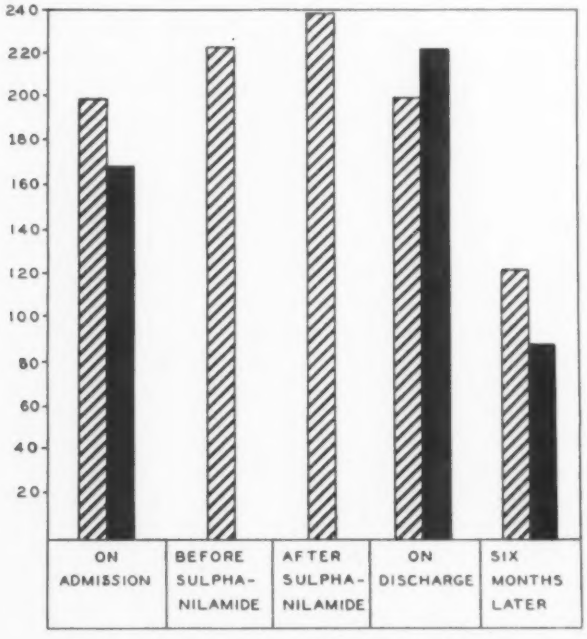

FIG. 2.—Units of antistreptolysin in blood serum.

each group whose urine became free of formed elements. It may also be noted that at the end of 6 months several others had entered this category. Of 33 patients in Group I examined at the end of 6 months there was a slight increase in the formed elements in 7 and a moderate increase in 2. Of 55 patients in Group II, 8 showed a slight increase, 4 moderate and 1 marked.

There were 9 (24%) of the patients in Group I who showed no

albumin nor formed elements at the time of discharge. In comparison there were 10 (14%) in Group II. At the time of discharge, there was more than 1+ albuminuria or 1+ formed elements in the urine of 7 (18%) of the 38 patients examined in Group I, and 28 (40%) of 70 in Group II. At the end of 6 months there was no albumin nor formed elements in the urine of 15 (45%) of 33 patients in Group I, as compared with 12 (22%) of 55 in Group II.

A common observation following tonsillectomies is to note an increase in the amount of formed elements and albumin in the urine. This is sometimes quite marked. In our control group of 70 patients tonsillectomies were performed on 38. In 29 (75%) of these there was a definite exacerbation (usually transitory) in the nephritis, being marked in 6, moderate in 15, and mild in 8. The subjects who received sulfanilamide offer a striking contrast to this in that exacerbation occurred in only 4 (14%) of the 29 patients who had tonsillectomies. The reaction was severe in 1, moderate in 1, and mild in the other 2. Worthy of mention is the fact that 3 of these patients had received no sulfanilamide for a month preceding operation. It should also be pointed out that the total intake of the drug was below average (49 gm.), being 18 gm. in 1 case and 27 in the other 2.

(*b*) *Renal Function.* The urea clearance was found to be impaired to about an equal extent in the two groups at the time of admission (Fig. 3, Table 3). This test showed that the renal function did not decrease in association with the sulfanilamide treatment

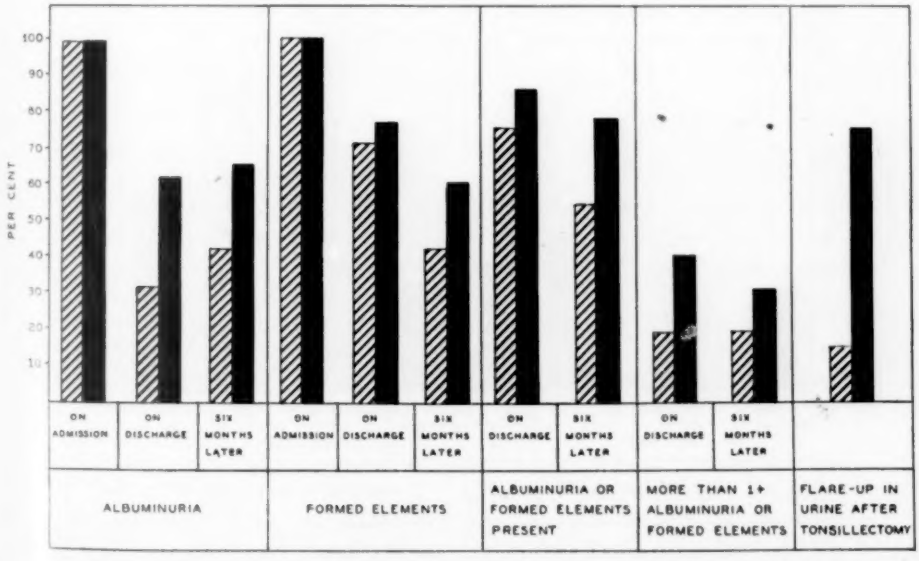

FIG. 3.—Percentage of patients showing albumin or formed elements in the urine,

in any instance. Indeed, before this therapy was started there were only 24% of the patients with a clearance above 75% of normal, whereas on the completion of this treatment there were 42%. At the time of discharge there had occurred a further improvement in each group, 48% in Group I having a function above 75%, as compared with 40% in Group II; at the end of 6 months this degree of function had been attained by 58% in the former group, as contrasted with 33% in the latter.

TABLE 3.—CHANGES IN UREA CLEARANCE.

Per cent of normal.	Less than 35.	35–45.	45–55.	55–65.	65–75.	75+.	Total.
On admission:							
Group I	4	4	4	7	4	9	32
Group II	5	13	6	8	9	11	52
Before sulfanilamide	3	4	5	4	5	7	29
After sulfanilamide	1	4	1	5	7	13	31
On discharge:							
Group I	1	1	4	5	5	15	31
Group II	2	4	7	10	5	19	47
Six months later:							
Group I	0	0	1	1	3	7	12
Group II	0	0	0	5	7	6	18

The phenolsulphonephthalein test showed the kidney function to be less impaired at all times than did the urea clearance (Fig. 4). On admission, 56% of the patients in Group I and 28% of the ones in Group II excreted more than 70% of the dye in 2 hours. At

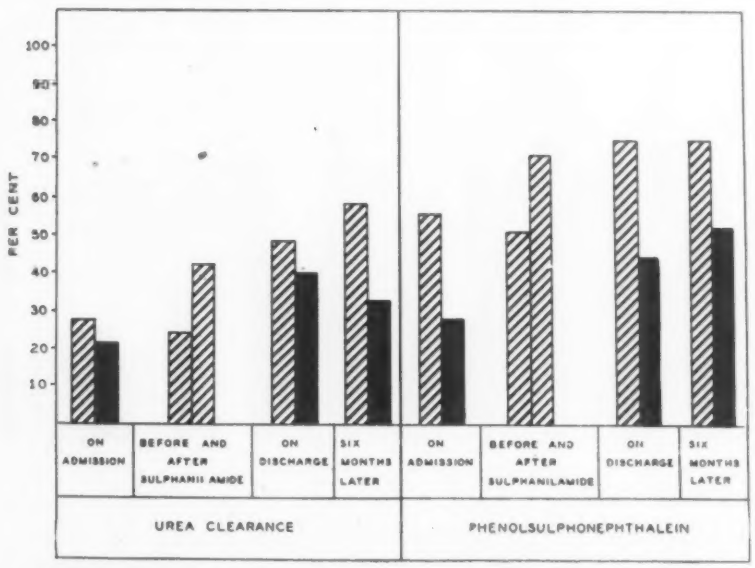

FIG. 4.—Percentage of patients with urea clearance greater than 75% of normal or phenolsulphonephthalein excretion greater than 70% in 2 hours.

discharge, there were 75% in Group I and 44% in Group II that excreted this quantity of dye. Examination of some of these patients 6 months later showed this percentage to be 75 in Group I and 52 in Group II. Before sulfanilamide was started, 51% of the subjects in Group I had a function above 70% and at the conclusion of this therapy there were 71%. In only 1 case did this test show the function to be lower at the end of treatment than at the beginning.

Duration of Edema and Hypertension. The edema was found to be of shorter duration in the subjects treated with sulfanilamide than in those not receiving this drug. In the former group it averaged 16 days, though varying from 2 to 135 days, while in the latter group it averaged 20 days with a variation of from 2 to 95 days. There was no demonstrable edema at any time in 7 subjects in Group I and in 9 subjects in Group II.

It was observed that in most instances, in each group, the disappearance of the edema was associated with a disappearance of the hypertension and, as was the case with the edema, the hypertension was of shorter duration in the group treated with sulfanilamide than in the control group, averaging 15.8 days in the former, with a variation of from 2 to 40 days, as compared with an average of 25 days and a variation of from 3 to 95 days. There were 13 in Group I who never exhibited any hypertension. In 1 instance the elevation of blood pressure persisted for 3 months (this patient is not included in the above average). At discharge and 6 months later, only 1 of the patients in Group I had hypertension. There were 14 subjects in Group II who never exhibited any hypertension and there were 7 who maintained an elevation in their blood pressure throughout their stay in the hospital. Six months later 4 of these continued to have this elevation whereas in 2 it had disappeared. The other patient did not return for examination.

Clinical Outcome. In attempting to evaluate the final outcome in these two groups of nephritis, it is desirable to consider first the number of deaths that occurred in the acute phase of the illness. During this stage, there are usually several factors that play a part in the fatal termination. In many patients the severity of the infection itself is of paramount importance; in some acute myocardial failure leads to a fatal termination; and in others symptoms of uremia are predominant, while in most instances acute anuria is present before death.[23]

It is apparent, therefore, that control of the acute infection and relief of the acute myocardial failure, if successful, may save the life of the patient.

It has appeared to us that the employment of sulfanilamide and the use of digitalis may have had this result in a few of the patients in Group I (Fig. 5). There was only 1 death in this group of 42 patients during the acute phase of the disease. This occurred in a

man 63 years of age with a deep infection of the thigh, not proven to be caused by hemolytic streptococci. In Group II there were 12 deaths (11%) during the acute phase. Five patients had severe hemolytic streptococcic infections of the throat accompanied in 1 by suppurative cervical lymph adenitis and complicated in all by pneumonia. One patient died in uremia with acute infection of the facial sinuses due to beta hemolytic streptococci. In 2 patients the acute nephritis followed scarlet fever, with complicating hemolytic streptococcic infections of the throat and ears during which time death resulted from uremia with myocardial failure. One patient died of pneumonia and pericarditis, 1 of acute streptococcic infection of the throat complicated by measles and hyperthyroidism, 1 from uremia and myocardial failure associated with a hemolytic streptococcic infection of the throat complicating sickle-cell anemia, and 1 from acute cardiac failure and nodal rhythm.

It is not inconceivable that if the newer chemotherapeutic measures had been available when these patients came under observation, the lives of some of them might have been saved.

These deaths account in part for the comparatively low recovery rate in the control group; but they are not entirely responsible since the beneficial effect of sulfanilamide is manifested not only by the distinctly lower death rate during the acute phase, but also in modifying the subsequent course of the disease.

Though it is admittedly difficult to determine accurately when complete healing of the nephritis has taken place, we have established the following criteria as being satisfactory for this purpose: The concentrated specimen of urine must be free from albumin, red blood cells and casts on more than one examination, often several, made at different intervals; or the Addis count must be within normal limits; the blood pressure must be within normal limits, and the urea clearance and phthalein excretion normal. Many of the patients whom we have considered as cured have been submitted to these tests on several occasions without showing abnormalities. A few patients have shown normal Addis counts when resting quietly in bed, but have voided urine when up and about that contained traces of albumin and small numbers of red blood cells. These patients have been classed as individuals in the latent stage of the disease.

Using these criteria for the basis of classification, 29 (74.3%) of the total number of 39 patients treated with sulfanilamide who have been followed for at least 2 years are well, whereas only 56 (52%) of the 108 control patients followed for at least the same period of time have recovered (Table 4). In Group I there are 7 patients (16.6%) of the total number of 42 who are now in the quiescent stage. Three of these have been observed for only a few weeks so that the final outcome cannot be determined. Two of these have improved rapidly, 1 has done poorly. Two of the

39 patients in Group I are, after 2 years, progressive. None has died in the chronic stage of the disease.

In the control group, 11 patients (10% of the entire 108) are in the quiescent stage and 29 (27%) have progressed to a chronic stage, from which 5 of these 29 individuals have died.

TABLE 4.—CLINICAL OUTCOME OF PATIENTS FOLLOWED FOR 2 YEARS OR LONGER.

	Group I.		Group II.	
	No.	%.	No.	%.
Well	29	74.4	56	52.0
Latent	7	18.0	11	10.1
Progressive	2	5.0	24	22.2
Dead	1	2.6	17	15.7
Total	39	100.0	108	100.0

Discussion. On the basis of the foregoing facts, it seems reasonable to conclude that in most respects the 42 patients receiving sulfanilamide have shown more rapid improvement than the 108 control individuals observed for a similar length of time. This has occurred in spite of the fact that in the two groups there has been relatively little difference as regards the type or severity of the initial infection, the interval from the infection to the onset of the nephritis, the type or the severity of the nephritis, or the interval from the onset of the nephritis to the admission of the patient to the hospital. Furthermore, other forms of treatment have been essentially the same in each group. In association with the use of sulfanilamide there has occurred, in most instances, a great reduction in the number of beta hemolytic streptococci in the throat or other foci of infection. This antibacterial effect apparently did not interfere with the immunologic response, as exhibited by the antistreptolysin titer of the blood serum, inasmuch as the quantitative changes in the serum bore the same relationship to the course of the disease in Group I as in the controls. The albumin and formed elements disappeared from the urine faster in the former groups; the kidney function, as indicated by the urea clearance and phenolsulphonephthalein tests, exhibited a definitely greater improvement; and the edema and hypertension were of shorter duration. Finally, of greatest importance was the fact that the incidence of recoveries was greater and the number of patients pursuing a progressive course distinctly less in the group that received sulfanilamide therapy.

Contrary to our expectations, we were not successful in rendering the tonsils free of beta hemolytic streptococci in more than one-half the cases. We can reconcile this with the clinical improvement, and the smaller number of exacerbations in the nephritis following tonsillectomy, only by assuming that the sulfanilamide had exerted in the tonsils its usual rôle of bacteriostasis.

To state precisely the mechanism by which sulfanilamide has

effected an improvement in the inflammatory reaction in the kidney is not possible, inasmuch as the etiology of acute hemorrhagic nephritis has not been proved. Since there is very good presumptive evidence, however, to show that acute nephritis is associated with hemolytic streptococcic infections (usually in the upper respiratory tract), since sulfanilamide has proved to be a potent defense against this organism regardless of where the infection lies, and since it is

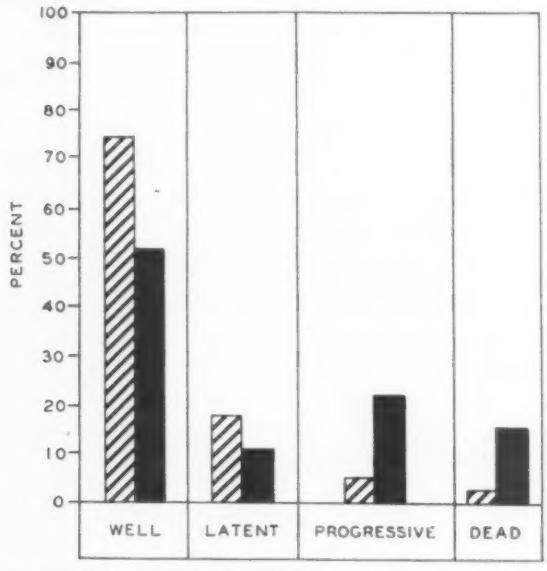

FIG. 5.—Clinical outcome of patients followed for 2 years or longer.

believed that the disappearance of infection and of this organism was related to recovery, there is reason to suppose that the beneficial effect of sulfanilamide resides in its antibacterial action on the infection.

Frequent urinalyses and kidney function tests failed to demonstrate that sulfanilamide had caused any renal damage either in these or in other patients. This is true in spite of the fact that most patients had edema, hypertension, large quantities of albumin with formed elements in the urine, and an elevation of the nonprotein nitrogen of the blood at the time that chemotherapy was started.

Sulfanilamide should be given for several days preceding and following tonsillectomy. It is useful to follow the same principle in association with other surgical procedures.

Owing to the fact that it was desirable to employ sulfanilamide with some caution in these patients many of them were not treated

with entire satisfaction. The drug was usually stopped when fever or nausea developed, and it now appears that the amounts of sulfanilamide employed were sometimes unnecessarily large. Frequently, again, the drug was not given over a sufficiently long period in small doses of 1.5 to 3 gm. a day. It may well be desirable to institute during the period of convalescence a form of therapy similar to that devised by Thomas and France[21] and by Coburn and Moore[1a,b] in their effort to prevent recurrences of rheumatic fever. In their hands the method has been highly successful and promises to be of signal value in the prophylactic treatment of rheumatic fever. It is our intention to adopt this procedure and to administer doses of sulfanilamide varying from 1.5 to 3 gm. a day over long periods of time following recovery from the acute phase of the disease, or possibly until all evidence of disease of the kidney disappears. It is hoped that by this means the duration of the disease may be shortened, recrudescences of hemolytic streptococcic infection prevented and the number of final recoveries increased.

Conclusions. A comparative study has been made of the course of acute hemorrhagic nephritis in a group of 42 individuals treated in essentially the same manner as a group of 108 similar individuals, except that in the former group sulfanilamide was administered. Most of these patients have been followed from 2 to 5 years or longer.

The results indicate that in the subjects receiving sulfanilamide the foci of infection have cleared up more rapidly, the signs of renal damage have disappeared more rapidly, the exacerbations of the nephritis following tonsillectomy have occurred less frequently, the duration of the edema and hypertension have been shorter and the clinical recoveries have been greater.

In the group of 42 patients treated with sulfanilamide there was 1 death in the acute stage. Complete recovery occurred in 15 of 33 cases who returned for observation after 6 months and in 29 of the 39 patients, or in 74.3% of those followed for at least 2 years. Three additional patients who have been followed for only a few weeks are in a quiescent stage. Five of the 39 patients are in the quiescent stage, and 2 are in a progressive stage.

In the control group of 108 patients, on the other hand, there were 12 deaths in the acute stage, and 5 deaths following a progression to chronic nephritis. Of the entire group of 108 patients there are only 56 complete recoveries, giving a percentage of 52; 11 patients are in the quiescent stage, and 24 in the chronic progressive stage of the disease.

The course of the immunologic reactions as exemplified by the antistreptolysin titer of the blood serum has been practically the same in both groups.

There was no evidence that sulfanilamide caused renal damage in any case.

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THE EFFECT OF VARIOUS SULFONAMIDES ON HEMOLYTIC STAPHYLOCOCCUS MEASURED WITH THE MANOMETRIC TECHNIQUE.

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In previous papers on the effect of various sulfonamides on the growth rate of *Brucella melitensis* and of pneumococcus,[1,2] we discussed the advantages of the manometric technique of measuring the bacterial metabolism quantitatively under physiologic conditions, as compared with the conventional bacteriologic methods of culturing and counting the bacteria. In this paper we are reporting the results of manometric determinations of sulfonamide effects upon the growth rate of staphylococcus.

Experimental. Very young cultures of three strains of hemolytic *Staphylococcus albus* and *aureus* were examined. They were isolated from the blood of a staphylococcus endocarditis, from the pus of a diabetic patient

with furunculosis and from a conjunctivitis exudate. Beef infusion-0.5% glucose-1% Difco-Bacto-peptone broth (pH 7.4) was used as culture medium. Rough differences in the number of bacteria were measured with the photronreflectometer (Libby). The bacteria volume was determined in the hematocrit by centrifuging aliquot parts of the bacterial suspension.

Since measuring the number and volume of the bacteria with the photronreflectometer and the hematocrit gives no information about the activity of the bacteria, the metabolism of the staphylococcus culture to be used was measured in a preliminary manometric experiment. In this, the oxygen consumption of one or two colonies of a 10- to 24-hour-old blood agar culture suspended in glucose-peptone broth was recorded (1 to 3 hours) until active growth was quantitatively established. These cultures of definite age and activity were used for making the suspensions for the final experiments with the sulfonamides.

Conical manometer vessels of 18 to 20 cc. capacity contained 2 cc. of the bacteria suspension in the main space. In the aërobic experiments the side bulbs of the manometer vessels contained 0.2 cc. 20% NaOH, and the oxygen consumption of the cultures was measured either in air or in other O_2/N_2 mixtures. In the anaërobic experiments the medium was buffered with 0.01 to 0.025 M sodium bicarbonate and the CO_2 formation was measured at various CO_2 concentrations in nitrogen. The temperature was 38° C.

The drugs tested were sulfapyridine sodium (sodium 2-sulfanilyl amino-pyridine monohydrate, Merck), sulfaguanidine (sulfanilyl guanidine, Lederle), sodium disulon (sodium sulfanilyl sulfanilamide, Alba Pharmaceutical Co.), sulfadiazine (2-sulfanilamido-pyrimidine, Lederle), sulfathiazol (2-sulfanilamido-thiazol, Winthrop), and sulfathiazol sodium (sodium 2-sulfanilyl-aminothiazol sesquihydrate, Squibb). In testing the potency of the various drugs one should avoid using relatively small quantities of bacteria with relatively high concentrations of drugs, and low concentrations of the drugs with large quantities of bacteria, since in the first instance the same strong inhibitory effect is seen no matter what drug is used, and in the second, no inhibitory effect can be seen at all. One must therefore vary drug concentration and bacteria inoculum until maximal discrepancies in the effectiveness of the various drugs in equal or different concentrations become apparent.

Figure 1 shows a typical experiment that complies with these conditions. The potency of the various drugs can be read from the figures obtained for the oxygen consumption of a staphylococcus culture, recorded every 15 minutes. The percentage concentration of the various drugs used was 0.5 mg. per 100 cc. The initial density of the suspension was 700,000 organisms per cc. The original culture was 1 hour old. The least effective of the drugs tested was sulfaguanidine. After 4½ hours the oxygen consumption was 665 c.mm. per hour as compared to 865 c.mm. of the drug-free control. Next in potency was sulfapyridine sodium (623 c.mm. O_2 consumption per hour), then sodium disulon (534 c.mm.), and sulfadiazine (402 c.mm.). The most effective was sulfathiazol sodium and sulfathiazol (182 and 203 c.mm.). The number of bacteria

grown, even after so short a period, was in sulfadiazine more than twice, and in sulfapyridine sodium more than three times the growth in sulfathiazol.

It is worth emphasizing that in the three strains of staphylococcus tested, sulfadiazine had a greater growth-inhibiting effect than sulfapyridine sodium, whereas in the case of pneumococcus (Types I, II, III), examined under the same experimental conditions, sulfapyridine sodium proved definitely superior to sulfadiazine. For both bacteria, sulfathiazol was the most potent growth inhibitor.

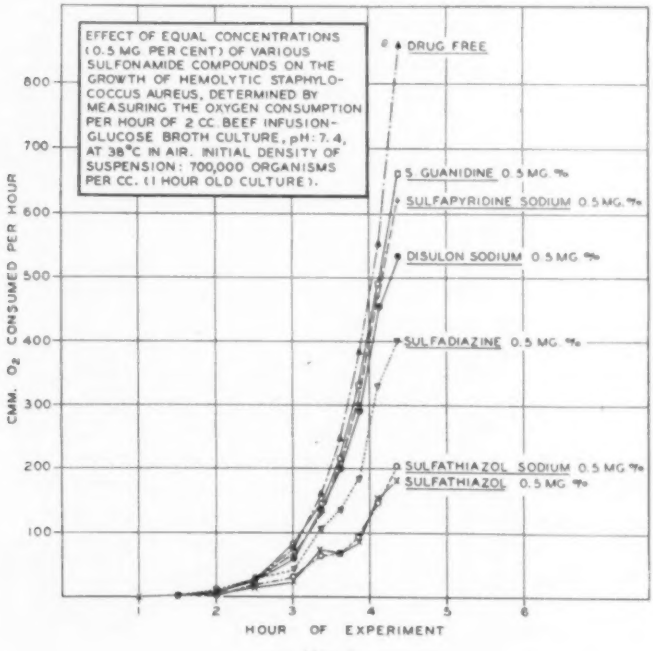
EFFECT OF EQUAL CONCENTRATIONS (0.5 MG. PER CENT) OF VARIOUS SULFONAMIDE COMPOUNDS ON THE GROWTH OF HEMOLYTIC STAPHYLOCOCCUS AUREUS, DETERMINED BY MEASURING THE OXYGEN CONSUMPTION PER HOUR OF 2 CC. BEEF INFUSION-GLUCOSE BROTH CULTURE, pH: 7.4, AT 38°C IN AIR. INITIAL DENSITY OF SUSPENSION: 700,000 ORGANISMS PER CC. (1 HOUR OLD CULTURE).
DRUG FREE
S. GUANIDINE 0.5 MG. %
SULFAPYRIDINE SODIUM 0.5 MG. %
DISULON SODIUM 0.5 MG. %
SULFADIAZINE 0.5 MG. %
SULFATHIAZOL SODIUM 0.5 MG. %
SULFATHIAZOL 0.5 MG. %
CMM. O2 CONSUMED PER HOUR
800
700
600
500
400
300
200
100
1
2
3
4
5
6
HOUR OF EXPERIMENT

FIG. 1.

Figure 2 shows the effect of 0.5 mg. per 100 cc. and 1 mg. per 100 cc. sulfadiazine and sulfathiazol on the staphylococcus growth rate. After 4½ hours the growth inhibition of 0.5 mg. per 100 cc. sulfadiazine was 61% and of 1 mg. per 100 cc. sulfadiazine 77%, whereas 0.5 mg. per 100 cc. and 1 mg. per 100 cc. sulfathiazol caused inhibitions of 83% and 84% respectively.

It seemed worthwhile to establish whether the growth-checking effect of the sulfonamides depends on an optimal oxygen concentration, like that of atmospheric air, or whether it can also be demonstrated at lowered oxygen concentrations and under anaërobic conditions. Figure 3 shows the effect of 3.3 mg. per 100 cc. sulfa-

thiazol on the staphylococcus growth rate in a beef-infusion-glucose-broth culture ($2.35 \cdot 10^{-2}$M $NaHCO_3$), determined by measuring the CO_2 formation at 5% CO_2/N_2 (pH 7.44). The initial density of the suspension was about 50 times as high as that in the foregoing experiments (37 million organisms per cubic centimeter). The original culture used as inoculum was 1 hour old. After an experimental

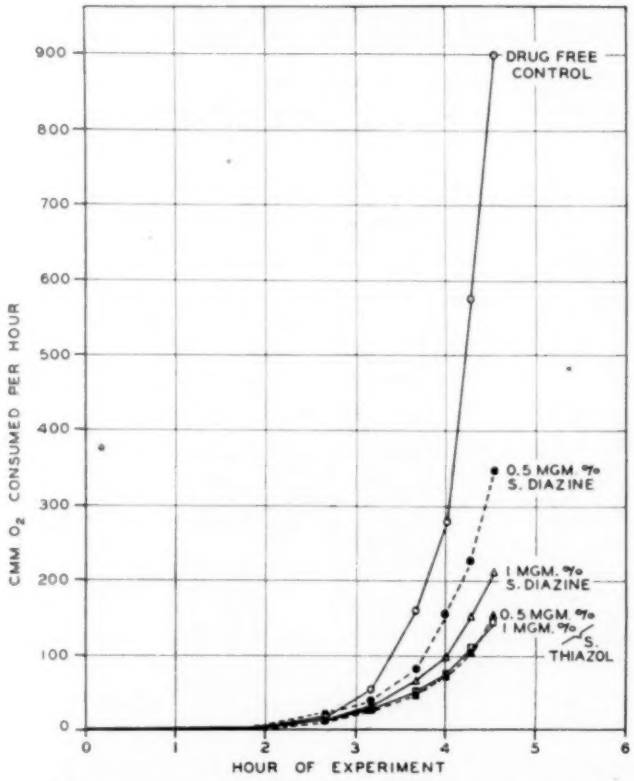

FIG. 2.—Effect of 0.5 mg. % and 1 mg. % concentrations of sulfadiazine and sulfathiazol on growth rate of hemolytic staphylococcus. Initial density of suspension: 740,000 organisms per cc. (1 hour old culture).

period of 3 hours, the drug-free control showed a growth of bacteria corresponding to a CO_2 formation of 264 c.mm. per hour, whereas the CO_2 formation in the sulfathiazol containing culture was only 52.5 c.mm. Under anaërobic conditions then, in spite of the large inoculum, a concentration of 3.3 mg. per 100 cc. sulfathiazol caused a growth inhibition of 80%. Sulfadiazine, sulfaguanidine and sulfapyridine sodium too exhibited a strong inhibitory effect on the

growth rate of staphylococcus under anaërobic conditions. In O_2 concentrations of 8 vol.% and 4 vol.% the inhibitory effect of the sulfonamides was likewise apparent.

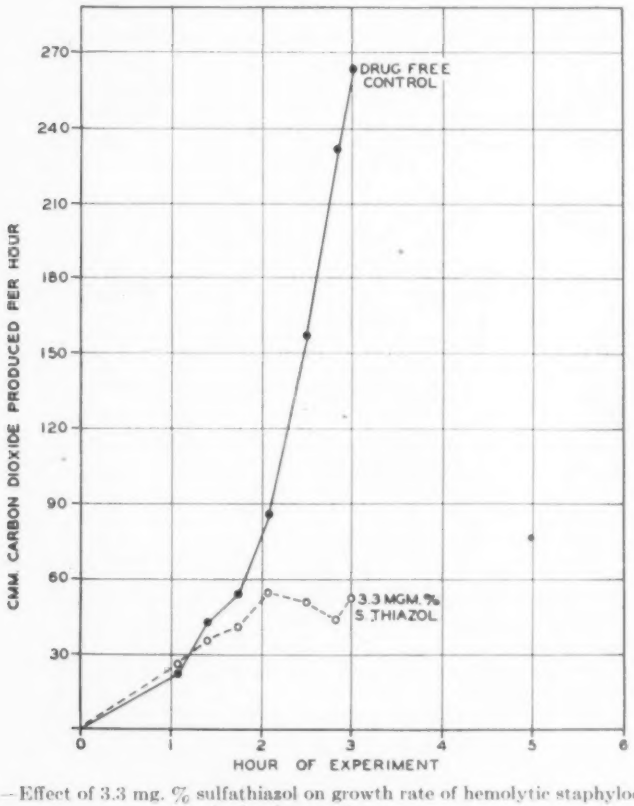

FIG. 3.—Effect of 3.3 mg. % sulfathiazol on growth rate of hemolytic staphylococcus *in the absence of oxygen.*

Summary. The effect of various sulfonamides on the growth rate of 3 pathogenic strains of hemolytic staphylococcus was determined by measuring manometrically the oxygen consumption and anaërobic CO_2 formation of glucose-peptone-broth cultures. The order of potency of the various drugs tested was as follows: least effective, sulfaguanidine with a bacteria growth after 4½ hours which corresponded to an oxygen consumption of 665 c.mm. per hour, as compared to 865 c.mm. of the drug-free control; then sulfapyridine sodium with 623 c.mm.; sodium disulon with 534 c.mm.; sulfadiazine with 402 c.mm.; and sulfathiazol and sulfathiazol sodium with 203 and 182 c.mm. respectively.

The amount of *staphylococcal* growth in sulfapyridine sodium was more than 200% in excess of that in sulfathiazol, while that in

sulfadiazine was only 100%. In *pneumococcus* cultures, examined under the same experimental conditions, sulfapyridine sodium was definitely superior to sulfa diazine. For both bacteria sulfathiazol was the most potent inhibitor.

By varying the concentrations of the drugs it could be shown that sulfadiazine was only half as effective as sulfathiazol as a growth inhibitor of staphylococcus. The sulfonamides inhibit the staphylococcus growth rate not only at optimal, but also at lowered oxygen concentrations, and under anaërobic conditions.

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CAVITY HEALING AND BRONCHIAL OCCLUSION.*

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The anatomy of healed cavities which up to a short time ago was a matter of conjecture can now be based on reliable observations followed up by Roentgen ray studies and necropsy. The number of such cases, however, is still small and there is much speculation as to the complicated series of events leading to closure or elimination of cavities. Three anatomic forms of healed cavities can be differentiated: 1, The solid focus due to retention, inspissation and final calcification of the cavity contents; 2, the radiating scar; 3, the bronchiectatic area remaining after the substitution of caseous and tuberculous elements in the cavity wall by ordinary granulation tissue, with subsequent epithelialization and fibrous shrinking of the space.

No figures are available assessing how often one or the other type of change occurs in cavity healing. All this justifies adding to our previous report (Pagel and Simmonds[12]) a further series illustrating the anatomy and development of cavity healing.

Case Reports. Case 1.—R. R., female, aged 14, had cough for 1 year with sputum positive for tubercle bacilli, and advanced tuberculosis in each lung with cavities (probably 3 or 4 in the left lung) each of approximately 1 to 1½ inches in diameter. Patient was treated by strict rest for 4 months,

* Owing to postal difficulties, proof of this article was not returned to the author for correction.

then left artificial pneumothorax (Dec. 9, 1938) and right artificial pneumothorax (Dec. 28, 1938) in view of grave prognosis. Cavities still present on Jan. 1, 1939. Died, Feb. 6, 1939.

Necropsy revealed in the subpleural ventro-axillary aspect of the left upper lobe, 3 soft caseous but solid foci with a fibrotic capsule, 0.2 cm. thick. Two were in the subapical and infraclavicular region and one in the lower parts of the upper lobe near the interlobar fissure. This focus was larger than the others. Its largest part belonged to the dorsal portions of the lobe. In the ventral parts it forked and was seen in a section as two partly separated foci. Its contents were softer than those of the apical foci, consisting of caseous, necrotic, partly edematous material rich in leukocytes, poor in tubercle bacilli, and lacking collagenous and elastic elements. Similar material was found in the large bronchi leading to the focus. In the formalin specimen it tended to retract from the periphery. The lung tissue surrounding the apical and subapical foci was aërated and slightly emphysematous, whereas the dorsal parts of the lower and largest focus were in collapsed and indurated lung parenchyma.

Obviously the solid foci correspond in size and situation to the three cavities seen in the roentgenograms. *The cavities were, therefore, converted into solid foci.* The last roentgenogram was taken 4 weeks before death. This case thus affords an opportunity of estimating the *minimum time necessary for the disappearance of a cavity.* It should be noted that the cavities brought to closure were of considerable size, the lowest one reaching a diameter of about 1½ inches.

Case 2.—N. Q., female, aged 17, had tuberculosis for 1 year, with right artificial pneumothorax in June, 1937, for hemoptysis. A cavity was present in right lower zone, and had spread on left side in 1938. Patient died following spontaneous pneumothorax on left side (Dec. 9, 1938).

A cavity in the right lower lobe (Figs. 1 and 2) disappeared between the roentgenograms of Dec. 10, 1937, and May 26, 1938; it was much smaller in the roentgenograms of July 6 and Sept. 13, 1937 (in spite of neighboring infiltration). It was still smaller in the roentgenogram of Oct. 18, 1937 (after absorption of neighboring infiltration).

Necropsy. In the dorsal portions of the right lower lobe, lung tissue was collapsed and indurated and contained an old caseous encapsulated focus the size of a bean (Fig. 3). Several similar but smaller nodules were found, one in the apex and another in the more caudal parts of the lower lobe. In addition, a complete and calcified primary complex was detected in the right lower lobe and corresponding hilar gland. No cavity was visible in the right lung.

The area of induration containing an old caseous encapsulated focus in the right lower lobe obviously corresponds to the cavity followed up in the roentgenograms until disappearance. According to radiologic evidence the conversion of the cavity into a solid focus was achieved in less than 5 months. It was a fairly large and not a thin-walled cavity and had been greatly reduced in size 2 months after pneumothorax was induced.

Case 3.—M. B. W., female, aged 38, had bilateral pulmonary tuberculosis for 3 years, with cavity in right upper lobe, diameter 1½ inches (Fig. 4). Sputum tubercle bacilli positive. Extrapleural pneumothorax in November, 1937. Cavity not seen thereafter (Fig. 5). Patient died, Jan. 21, 1940, following spontaneous pneumothorax on the left side.

Necropsy. The right upper lobe especially in the apical part was greatly shrunken, the pleura being about 1 cm. in thickness. The dorsal parts contained besides a subpleural emphysematous bulla and a few small scattered caseous nodules, an old caseous round focus with a thin capsule. The ventral parts of the caseous round focus connected with a bronchus filled

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

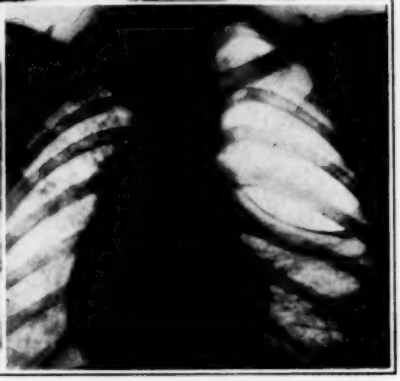

Fig. 1.—Case 2 (July 6, 1937). Right lung. Cavity in lower zone.

Fig. 2.—Case 2 (July 27, 1938). Cavity disappeared.

Fig. 3.—Case 2. Solid focus in lower part of right lower lobe corresponding to site of cavity. No cavity visible.

Fig. 4.—Case 3 (May 26, 1937). Large cavity in the infraclavicular part of the left upper lobe.

Fig. 5.—Case 3 (April 13, 1939). Extrapleural pneumothorax. Cavity disappeared.

with old caseous material and therefore very similar in nature to the round focus itself (Fig. 6). This area of caseous bronchitis was most impressive. The round focus and caseous bronchitis were obviously the remains of the cavity shown in the original roentgenogram and disappeared after extrapleural pneumothorax treatment.

Case 4.—B. M., male, aged 26, had tuberculosis involving both lungs for 2½ years. In the right side, he had a large cavity below the clavicle (2½ inches in diameter), and on the left side, three cavities were present, each about 1 inch in diameter, one just below the clavicle and the others more caudally (Fig. 7). A left pneumothorax was induced (March 8, 1940), and the upper and lowest cavities were thereafter no longer visible, although the middle cavity persisted (Fig. 8). This cavity ruptured after the adhesion over it had been divided.

Necropsy. The subapical region of the left upper lobe contained an encapsulated caseous focus which was round in the dorsal parts and oblong in the more ventral aspects. The capsule was thin, 0.2 cm. in width, the surrounding lung tissue emphysematous and not collapsed or indurated. (*a*) The cavity which the roentgenogram showed in the infraclavicular parts of the left lung was obviously substituted by a solid round and partly oblong caseous focus. A tear into the middle part of the upper lobe (*b*) was present at the site of the central cavity (spontaneous pneumothorax). Another solid focus represented the lowest cavity (*c*) (Fig. 9).

Case 5.—R. H., male, aged 23, had tuberculosis of left lung for 3 years with several cavities, and was treated by artificial pneumothorax and adhesion section (June, 1937). Spread of disease noted in right lung, so left artificial pneumothorax was abandoned in May, 1940, and right artificial pneumothorax begun. Death resulted from right spontaneous pneumothorax. Roentgenogram, May 18, 1938: Extensive cavitation left upper lobe, uncollapsed by pneumothorax. Roentgenogram, July 13, 1940: After artificial pneumothorax cavitation right upper lobe, no obvious cavity on left side.

Necropsy revealed a small shrunken cavity the size of an almond in the dorsal parts of the right upper lobe, near the interlobar fissure. The cavity was almost completely filled with inspissated contents, but still contained a small lumen which did not communicate with the bronchial system.

Left lung: The upper lobe contained three well-encapsulated round foci with adjacent caseous bronchitis and in addition a few smaller nodules, but there was no cavity visible. The lung, as a whole, was shrunken and the pleural membrane thickened.

The cavities visible in the roentgenogram in the left upper lobe were replaced by solid round foci, whereas there was still a remnant of the cavity in the right upper lobe. The cavity in this part, however, is considerably shrunken, almost filled with inspissated contents and does not communicate with the bronchi. It may be assumed that it would have closed completely if death had not intervened. The actual interval between the last roentgenogram showing a large uncollapsed cavity in the right lung and death was 3 weeks. Note that in this interval the cavity had nearly, though not completely, been replaced by a solid focus.

Case 6.—Male, aged 41. Roentgengram showed a cavity and infiltration in right mid-zone (Fig. 10). Right artificial pneumothorax begun in December, 1936, was followed by adhesion-section, and maintained for 4 years. Roentgengram in September, 1940, showed no lumen to an opacity representing previous cavity and infiltration (Fig. 11). Died April, 1941. At necropsy, in the right lower lobe there was an old dry caseous, partly calcifying, nodule about 1 inch in diameter, with adjacent caseous calcifying bronchitis (Fig. 12). No cavity was seen in the right lung.

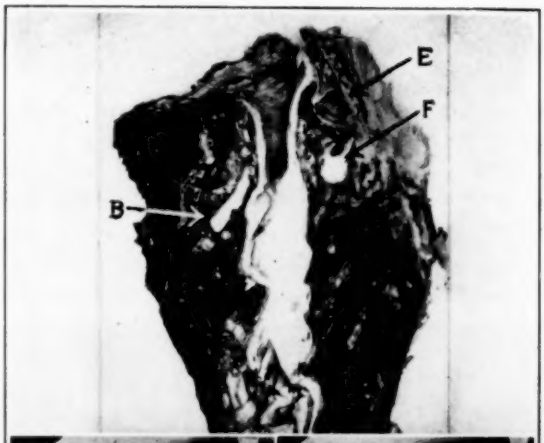

FIG. 6.

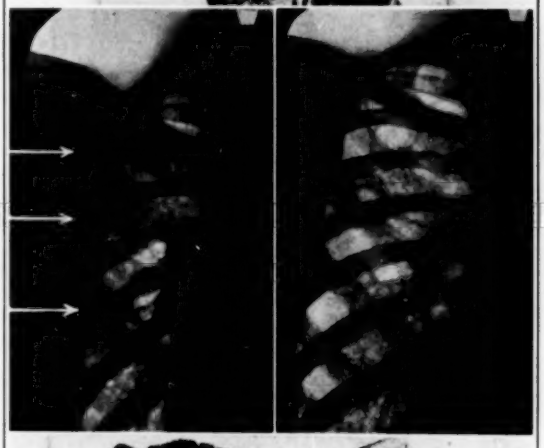

FIG. 7.

FIG. 8.

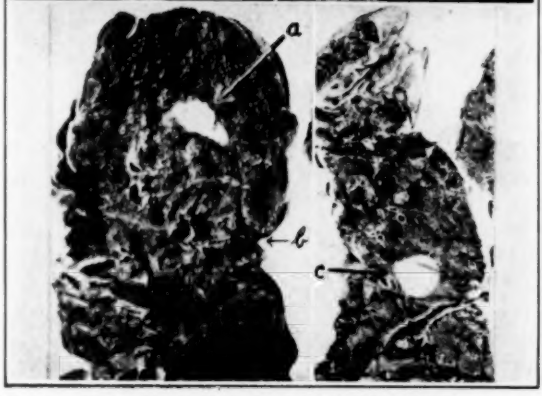

FIG. 9A.

FIG. 9B.

FIG. 6.—Case 3. Left upper lobe: *F*, Solid focus at the site of the cavity; *E*, emphysematous bulla; *B*, caseous bronchitis attached to focus.

FIG. 7.—Case 4 (Sept. 18, 1939). Left upper lobe showing three cavities (arrows).

FIG. 8.—Case 4 (June 21, 1940). Two cavities have disappeared; cavity in mid-zone persisting.

FIG. 9.—Case 4. Left upper lobe: (*a*) Solid oblong focus (caseous bronchitis) in the subapical parts corresponding to cavity shown in the infraclavicular area of Fig. 7; (*b*) slit-shaped collapsed cavity in mid-zone with perforation corresponding to mid-zone cavity in Fig. 8; (*c*) solid focus in lower part of left upper lobe corresponding to lower cavity in Fig. 7.

Discussion. All cases presented in this series are examples of cavity healing by conversion of the space into a solid, caseous and calcifying focus. At necropsy no cavity could be traced, but corresponding in situation, shape and size in the specimen was a caseous nodule looking like an ordinary "round focus."

FIG. 10 FIG. 11

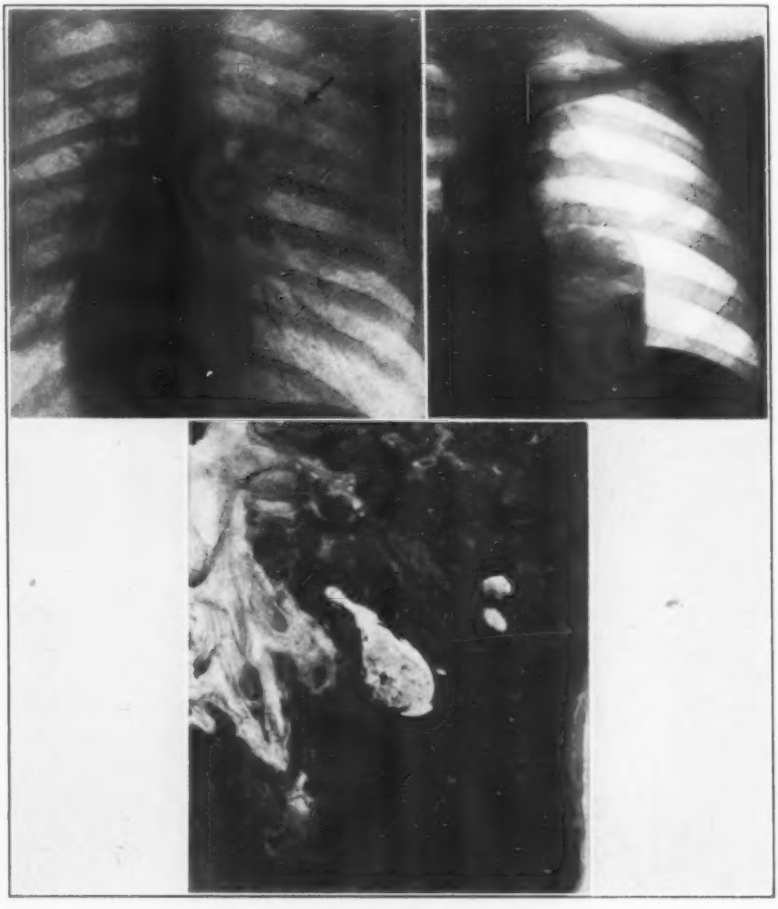

FIG. 12

FIG. 10.—Case 6. Oct. 17, 1936. Cavity (arrow) and infiltration in the right mid-zone

FIG. 11.—Case 6. Sept. 17, 1940. Large artificial pneumothorax right. Cavity replaced by solid shadow (?scar).

FIG. 12.—Case 6. Anatomic specimen of lower part of right upper lobe showing calcifying round focus with *caseous bronchitis* at site of cavity.

Various stages of the development are represented in the cases described. The last stage, *i. e.*, calcification, was traced through from the initial cavity in our observation reported in a previous paper (Pagel and Simmonds[12]).

In the present case, Case 1, the process of closure must have been very recent. The roentgenogram still showed the cavities, but at necropsy, foci consisting of a soft caseous matter had taken their place. Two points are noteworthy in connection with this case: (*a*) The short interval of 4 weeks necessary for the conversion. In our previous series[12] (loc. cit., 1939, Case 4) a similar instance was reported and an interval of 2 months was found between the last roentgenogram still showing the ring shadows of cavities and the necropsy revealing soft, but solid nodules. Three months was the interval in the observation by Pagel and Roberts.[19] We are in accord with Pinner[14b] that the soft focus as seen in these cases may revert, and need not necessarily result in permanent closure, but it is, no doubt, an earlier stage of the older caseous and calcifying nodule which is found in securely stabilized, *i. e.*, healed cavities. (*b*) The same soft material as in the nodule was found in the bronchi leading to the closed cavities. One of them consisted in its whole ventral part of a system of bronchi with caseous material ("caseous bronchitis"). This shows the importance of the bronchi at an early stage in cavity healing. Even more pronounced was the caseous bronchitis in Case 3 which showed a more advanced stage with beginning calcification of the closed cavity.

The same prominence of caseous bronchitis attached to closing or healed cavities has been noted in our previous series[12] (loc. cit., 1939, Cases 2 and 3) and it appears to be an essential feature. Only in the present Case 2, we found no caseous bronchitis, the bronchi leading to the closed cavity being obliterated, ending blindly in the fibrotic capsule.

Such frequent observation of an area of caseous bronchitis immediately connected with the closing or healed cavity has not been recorded in the few anatomic cases of closed cavity healing which have been described, although it has been emphasized that there was no communication of the focus with the main bronchi (Wurm,[16] Auerbach and Green[3]). Our findings are, however, important in the light of Coryllos' theory which regards early bronchial closure as the main factor in cavity healing. Pinner[14b] has also recently given a qualified support to his view. The pictures presented in this paper are evidence in favor of this theory. It cannot be assumed that the bronchial changes are secondary to cavity closure for the following reason: If early infiltrations of the Assman type or early "round foci" are examined anatomically caseous bronchitis will be found connected with the focus in practically all cases, and in some of them forms the main part of the changes or the lesion

itself. If cavity formation occurs, liquefaction manifests itself first and most intensely in the focus and secondarily, to a lesser degree, in the caseous bronchus leading to it. This is probably due to multiplication of tubercle bacilli in the focus and not in the bronchus. It is obvious that after liquefaction of the central focus the bronchus often retains a considerable quantity of caseous material leading (particularly after induction of collapse therapy) to occlusion and kinking of its lumen with all consequences of cavity collapse, retention of cavity contents and healing, such as visualized by Coryllos. Thickening of the bronchial wall by tuberculous infiltration and edema increase the tendency to occlusion.

As a rule, caseous bronchitis which may thus lead to occlusion of the cavity is a diffuse lesion involving the bronchial wall in its whole length and not only a localized "bronchial plug" formed at the entrance of the bronchus into the cavity. Those authors who advocated the theory of cavity healing by bronchial occlusion suggested that a "bronchial plug" is responsible. Such "bronchial plugs" *do* occur. First anatomical evidence of this has been given by one of us (Pagel and Roberts[10]) in a case in which a "bronchial plug" accounted for distention and subsequent extensive collapse of a cavity and surrounding lung tissue.

These changes in the bronchi, beneficial when they lead to cavity healing, may be a most dangerous element in other cases when the bronchial lumen is partially obstructed and acts as a valve allowing air to enter, but not to leave the cavity. Such action leads to cavity distention, at times of severe degree. A liberal oxygen supply thus provided might accelerate the multiplication of tubercle bacilli and the breakdown of lung tissue. This, combined with intracavitary tension, leads to rupture and pleural contamination. It is shown by one of the cavities observed by Pagel and Roberts[10] which exhibited extensive caseous changes all along the wall of the draining bronchus and had ruptured in the course of artificial pneumothorax treatment and adhesion cutting. In this way serous effusion and empyema are produced. This complication is much more common when the cavity fails to close by pneumothorax therapy—in other words, when the cavity remains tense by the valvular action outlined.

In our view, the presence of tuberculous caseous bronchitis connected with a cavity has not been sufficiently emphasized. Not only in the stages of cavity healing described or in the gross complications mentioned above, but at all stages of cavity formation and development, does this bronchial lesion play its part. Particularly in the earlier and elastic stages of the cavity, bronchial tuberculosis with its valve mechanism causes the increase, and sometimes rapid variation, in cavity size. It accounts for the circular shape of cavities seen in the Roentgen ray film, though such cavities seen

in the cadaver may be irregular in shape due to postmortem diffusion of the air in them.

As to the question of frequency of the various forms of anatomic cavity healing, the present authors have now collected a total of 10 cases. In only 2 of them "open cavity healing" (*i. e.*, healing of the cavity wall with persistence of the hole) was observed, while 8 were examples of cavity closure by conversion into a caseous or calcifying nodule. There was, however, no example of healing by formation of a radiating fibrotic scar.* Although the number of cases is still small and hardly permits of a statistical analysis, healing by conversion of the cavity into a solid focus seems to be the most frequent anatomic basis of cavity healing.

TABLE 1.—TYPES OF CAVITY HEALING IN CASES WITH NECROPSY.

Authors.	Open cavity healing.	Radiating scar.	Conversion into solid focus.	Hydrops of cavity.
Gilbert[5]	..	1	1	
Pagel[9]	1			
Alexander[1]	1			
Graeff[6]	..	..	1	
McPhedran and Long[8]	..	1		
Sweany[15]	..	1		
Amberson[2]	..	..	..	1
Pagel and Robinson[11]	1			
v. Karwowski[7]	..	1		
Pinner[14a]	..	2		
Pinner[14b]	1	1		
Derscheid and Toussaint[4]	..	..	1	
Pagel and Roberts[10]	..	..	1	
Wurm[16]	..	3	1	
Pagel and Simmonds[12]	..	..	2	
Auerbach and Green[3]	1	1	3	
Pagel and Simmonds	..	..	6	
Total	5	11	16	1

Total of 33 cases.

The same conclusion emerges from a study of the literature (Table 1) and has been drawn by Auerbach and Green.[3] The frequency of cavity healing by conversion into a solid focus vindicates the assumption made by many clinicians for a long time that a calcified nodule often represents the last remnant of a healed cavity. This was often doubted and the calcified nodule regarded as ancient

* The 2 cases of open cavity healing are those described by Pagel[9] and Pagel and Robinson,[11] the others observed by Pagel and Simmonds.[12] Pagel and Simmonds' paper had been sent to press for a long time when the observations by Wurm[16] and Derscheid and Toussaint[4] appeared. Before this there was only one observation of cavity healing by conversion into a solid focus, that by Graeff.[6] The instance described by Amberson[2] shows a special form of cavity closure. It appears to be filled with a fluid rich in cholesterol crystals: "Hydrops of the Cavity." This may constitute an early stage of conversion into a solid focus, but in Amberson's case the hydrops had persisted for 10 years and it is unlikely that conversion would have occurred thereafter.

primary or postprimary foci appearing in the roentgenogram after the cavity has disappeared (Wurm[16]).

In the whole material of the present authors the healing of the cavity was spontaneous in only 1 case and in the other 10 collapse therapy had been employed (in 8 cases artificial pneumothorax, in 2 extrapleural pneumothorax).

Healing by conversion into a solid focus, as also that by formation of a radiating scar, obliterate the cavity; in open cavity healing a space persists. The first two methods of cavity closure may be grouped together, therefore, as far as the result is concerned. It is, however, doubtful whether they have anything else in common, notably in their pathogenesis. Nor is it conceivable that one form is the terminal phase of the other; in other words, solid caseous material which tends to calcification is unlikely to disappear completely and result in a fibrotic scar. It is more likely that either concentric fibrosis with a final scar, or inspissation of cavity contents without conspicuous fibrosis, occurs.

Why do some cavities heal by scar formation and others by conversion into a solid nodule? The answer to this question must remain a matter of speculation, but the following explanation is tentatively advanced. In our own series, pneumothorax was the means of therapy used. Following this operation there may be a rapid closure of the bronchus which has been already partially obstructed by caseation. The thick caseous lining of the cavity therefore does not have time to be discharged or to become absorbed, but absorption of the air in the cavity allows collapse and the caseous lining appears as a solid encapsulated focus. Where the bronchus is more patent, drainage is more free and there is less material to form a solid nodule. The closure of the cavity also may then be a slower process and be accomplished by concentric shrinking of the cavity wall by fibrosis and obliteration of the lumen with the final result of a scar.

In view of the rapid changes in size which cavities can assume (according to intracavitary pressure and the condition of the bronchi, as shown by the pioneer work of Pearson[13]) it is hardly justifiable to continue otiose considerations as to the maximum size of a cavity permitting of healing.

Summary. 1. A new series of 6 cases illustrating the anatomy of healed cavities is described.

2. All observations were examples of cavity healing by conversion of the space into a solid caseous nodule.

3. Four weeks appears to be the minimum time needed for this process.

4. Anatomic evidence was adduced that occlusion of the draining bronchi (either by obstructive caseous bronchitis or by formation of a caseous plug) is largely instrumental in this form of cavity healing.

5. Nine of 11 cases observed by the present authors and 16 out of 33 instances of anatomic cavity healing recorded in the literature, are examples of healing by conversion into a solid nodule. The frequency of this form vindicates the clinical assumption that not infrequently calcified nodules appear at the site of former cavities as the terminal stage of healing.

6. Conversion into a fibrotic radiating scar and into a solid focus differ in genesis and are identical only in the result—the disappearance of the actual space.

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HYPOPROTHROMBINEMIA IN PERNICIOUS ANEMIA.*

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The plasma prothrombin level is frequently 15% to 25% below normal in patients with chronic debility, despite administration of adequate amounts of vitamin K. This was found to be true of the nutritional deficiency states seen in the Nutrition Clinic of the Hillman Hospital at Birmingham, Ala. Similar values were obtained in many debilitated patients in the University Hospital at Iowa City. The combined results of both studies were recently reported.[6] In contrast to this mild hypoprothrombinemia, several patients with pernicious anemia, seen at the Hillman Hospital

* Aided by a grant from the John and Mary R. Markle Foundation; funds for technical assistance were supplied by the Graduate College, State University of Iowa.

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The plasma prothrombin level is frequently 15% to 25% below normal in patients with chronic debility, despite administration of adequate amounts of vitamin K. This was found to be true of the nutritional deficiency states seen in the Nutrition Clinic of the Hillman Hospital at Birmingham, Ala. Similar values were obtained in many debilitated patients in the University Hospital at Iowa City. The combined results of both studies were recently reported.[5] In contrast to this mild hypoprothrombinemia, several patients with pernicious anemia, seen at the Hillman Hospital

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through the courtesy of Dr. R. W. Vilter, were found to have only about one-half the normal amount of prothrombin.

In recent studies at the University Hospital we have extended these preliminary observations on pernicious anemia. In addition, we now have data to show that this hypoprothrombinemia is not appreciably affected by the administration of vitamin K. Following the institution of liver therapy, however, there is an abrupt rise in the prothrombin level.

Material and Method. Twenty cases of Addisonian pernicious anemia, admitted to the University Hospital, were made available for study by the staffs of the Departments of Medicine, Neurology and Urology. The diagnosis was based on the history, and the clinical and laboratory findings, together with the hematologic response to liver extract.

Twelve of the 20 cases received daily intramuscular injections of 1 to 5 cc. of liver extract (Lilly or Lederle, 15 U.S.P. units per cubic centimeter). Of these 12, 7 were given vitamin K for 3 to 6 days prior to the institution of liver therapy. As a source of vitamin K activity we administered 2-methyl-1, 4-naphthoquinone in 5 of the cases (6 mg. daily, given in corn oil, along with bile salts). Instead of this compound, 2 cases received daily intravenous injections of 1 mg. of 4-amino-2-methyl-1-naphthol ("Synkamin"*). Prothrombin determinations were made by the two-stage method of Warner, Brinkhous and Smith.[4,5a]

TABLE 1.—PROTHROMBIN VALUES IN PATIENTS WITH PERNICIOUS ANEMIA.

Case No.	Erythrocyte hematocrit, %.	Prothrombin, % of normal.	Central nervous system damage.†
1	11	40	++
2	14	46	++++
3	15	52	++
4	17	50	+
5	18	45	0
6	19	45	+++
7	19	52	+++
8	20	40	+++
9	20	56	++++
10	20	68	++
11	21	42	+
12	22	59	+++
13	23	47	+++
14	24	42	++
15	26	73	++
16	27	47	+++
17	29	43	++
18	29	60	++
19	31	82	++
20	35	58	++++

† Central nervous system damage estimated as follows: 0, no subjective or objective findings; +, paresthesiæ; ++, mild objective findings; +++, marked objective findings; ++++, cord degeneration to the point of paralysis.

Results. The prothrombin values obtained at the time of admission in this group of cases are shown in Table 1. The cases are listed in order of hematocrit values. Only 3 of the patients showed prothrombin values greater than two-thirds of the normal level, and in 10 (one-half of the cases) the values were less than one-half

* The "Synkamin" used in this study was kindly furnished by Parke, Davis & Co.

of the normal. There is some tendency for the lowest values to occur in the cases in which the anemia is severe. However, it is evident from the table that the degree of anemia and the degree of hypoprothrombinemia are not closely correlated. There is no correlation whatever between the degree of prothrombin deficiency and the amount of nervous system damage.

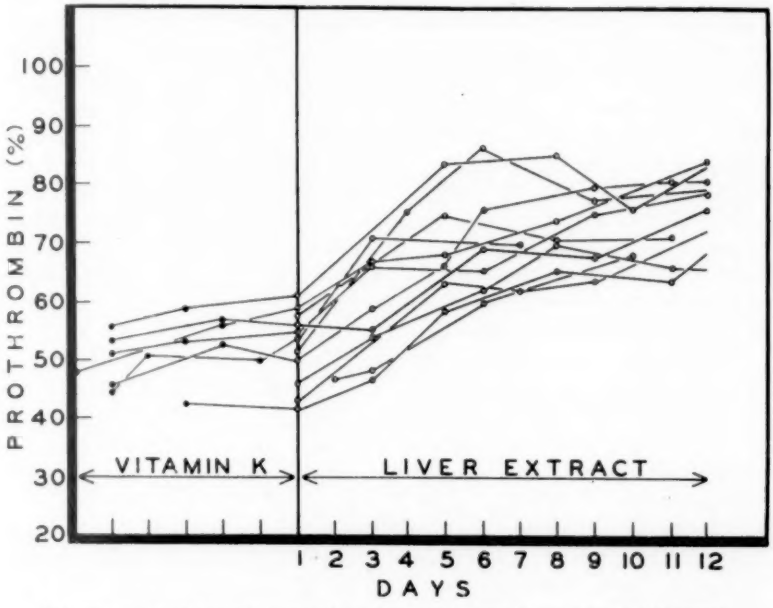

CHART 1.—Prothrombin response to therapy in pernicious anemia (12 cases).

The effect of therapy on the prothrombin level of the treated cases is shown in Chart 1. The first part of the chart shows that the administration of large amounts of vitamin K had no consistent influence on the prothrombin values. The very slight improvement seen in a few of the cases is not more than might result from general improvement incident to bed rest. The last part of the chart shows, in contrast, that the level rises rapidly following the institution of liver therapy. The rise was somewhat more rapid than the corresponding increase in circulating red cells, and was much greater than could result from simple concentration of the plasma due to increase in the hematocrit. Maximum prothrombin values, reached in about 1 week, were maintained. The prothrombin level did not, however, rise to quite normal values, and in general, the level ultimately reached was higher in the cases having the higher initial values. In the majority of the cases the daily dose of liver extract was 1 cc.; a few given larger amounts showed no greater prothrombin response.

Discussion. The lowest prothrombin value observed in these cases, 40% of normal, is above the level at which bleeding ordinarily occurs, and none of the cases showed any clinical evidence of hemorrhage. It is perhaps significant, however, that the clotting power of the blood, as measured by the one-stage prothrombin methods, is essentially normal. Thus, the prothrombin levels in these cases, by both the "bedside" test[8b] and by the method of Quick,[2] were found to be within normal limits, and were not modified by treatment. The biologic significance of the failure of the one-stage tests to agree with the two-stage method, in certain conditions, is not yet apparent. The suggestion of Quick and Grossman[3] that the two-stage method may be affected by variation in other plasma proteins receives no support in the present instance. Plasma protein determinations in a number of our cases yielded values for both the total protein and the albumin-globulin ratios which were within normal limits, and which were not altered by treatment. Perhaps some compensatory mechanism, as has been suggested in other conditions,[1,5b,8a] permits a more ready utilization of the prothrombin available in pernicious anemia.

The basic reason for the prothrombin fall reflected by the two-stage method is at present obscure. It is not obviously related to the anemia itself, for many long-standing cases of secondary anemia and of aplastic anemia show no depression whatever. Even in pernicious anemia the change is not clearly related to the degree of anemia.

The beneficial effects of liver therapy might seem to imply that the liver extract supplies some unknown factor needed for prothrombin production. However, it is, perhaps, even more likely that the rise in the prothrombin level is related to improvement in function of some organ—the liver for example. It is known that the liver is concerned in the manufacture of prothrombin, and studies on the excretion of urobilinogen[7] do, in fact, suggest mild hepatic insufficiency in cases of pernicious anemia. The prothrombin response in pernicious anemia may be related to the response in red cell production, but any such relationship is not yet apparent. In any case, the beneficial effect of liver extract on the production of prothrombin appears to be confined to cases of pernicious anemia. We have administered liver extract to newborn infants, as well as to patients with Laennec's cirrhosis and to patients with obstructive jaundice. The hypoprothrombinemia present in such cases did not respond to the liver extract. Likewise, the mild hypoprothrombinemia seen in debilitated patients does not respond to this form of treatment.

Summary. Patients with Addisonian pernicious anemia in relapse usually show considerable decrease in plasma prothrombin. In the majority of such cases, the prothrombin level is found to be between 40% and 65% of the normal. The hypoprothrombinemia is not rectified by large doses of vitamin K. When specific liver

therapy is instituted, the plasma prothrombin level promptly shows a marked rise.

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INFLUENCE OF ACTIVE AND INACTIVE ANTIANEMIC PRINCIPLES UPON THE ERYTHROCYTES OF THE IMMATURE OPOSSUM (DIDELPHYS VIRGINIANA).

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Because of certain similarities between the erythrocytes of mammalian fetuses and those of patients with pernicious anemia[9] attempts have recently been made to influence the rate of maturation of fetal erythrocytes by the experimental administration of antianemic principles to animals during gestation.[8] Adequately controlled studies have shown demonstrable changes in the peripheral blood and bone marrow of treated mothers, although this observation has not been confirmed by all observers. Schlicke,[6] in the largest series of experimental animals reported to date, has confirmed the original observation that normal gastric juice, when administered to pregnant albino rats, influences the rate of maturation of the fetal red blood cells. He also reviewed comprehensively the controversial observations of the various workers in this field, his review including all but the two most recent reports,[3,5] in both of which the writers failed to secure results by this method.

The inaccessibility of common mammalian fetuses to direct injection made it desirable to find a species in which antianemic principles could be injected directly into the developing animals rather than into the mothers. The marsupial opossum (*Didelphys virginiana*) is a suitable animal for this purpose, as we have pointed out in a preliminary study,[7] because in this species, after an intra-

uterine life of approximately 12 days,[2,4] the immature young live in the maternal pouch for 90 days. In this same study[7] we also reported observations which indicated that pouch opossums had a macrocytic anemia, as compared to adult animals, and that the direct injection of antianemic principles into the immature animals in the maternal pouch reduced the size of their erythrocytes.

Materials and Methods. The studies reported in this paper were carried out on 6 adult male opossums, 4 adult non-pregnant female opossums and 117 immature opossums. The immature opossums were contained in the pouches of 18 adult female opossums. The adult animals were trapped in Louisiana and Mississippi during the winter months of 1939 and 1940.

During the experimental period each adult animal was housed in a separate cage and fed a diet consisting of fresh Purina dog chow, bone meal, milk and water.

The number of young animals found in a single pouch varied from 5 to 9. Forty-nine were used in 1939. The crown-rump lengths of the animals in this year varied from 5.5. to 7 cm. and averaged 6.39 cm. at the beginning of the experiment. No significant variations were noted in the size of the litter mates. Sixty-eight animals were used in 1940. The crown-rump lengths in this year varied from 5.5 to 7 and averaged 6.62 cm. at the beginning of the experiment. Slight variations were noted in the size of the litter mates.

The animals in each pouch were divided into 2 groups, one of which consisted of treated animals and the other of untreated controls. Each animal was identified by an ear puncture.

The immature opossums in the various maternal pouches were divided into 5 groups, as follows:

Group I. Thirty-nine animals. Twenty experimental and 10 control animals were used in 1939, and the studies were repeated on 5 experimental and 4 control animals in 1940. The treated animals were given daily intraperitoneal injections of concentrated normal human gastric juice, in doses varying from 0.1 to 0.2 cc., for periods varying from 3 to 13 days. The total amount administered varied from 0.8 to 2.2 cc. The gastric juice, which was secured from normal subjects after injection of histamine, was prepared from several samples, which were pooled, filtered, concentrated 10 times by evaporation, and neutralized with NaOH just before being used. This material presumably contained the intrinsic factor of Castle; no attempt was made to determine the presence or absence of the extrinsic factor.

Group II. Twenty-six animals. Nine experimental and 10 control animals were used in 1939, and the studies repeated on 4 experimental and 3 control animals in 1940. The treated animals were given daily intraperitoneal or subcutaneous injections of a concentrated solution of liver extract (Lederle, 1 cc. containing 15 U.S.P. units),* in doses varying from 0.1 to 0.2 cc., for periods varying from 3 to 14 days. The total amount administered varied from 0.3 to 2.6 cc.

* Generously supplied by the Lederle Laboratories, Inc., New York.

Group III. Twenty-six animals, 16 of which were treated and 10 of which served as untreated litter mate controls. All the experiments were carried out during 1940. The treated animals were given daily intraperitoneal injections of inactivated concentrated normal human gastric juice, in doses varying from 0.1 to 0.2 cc., for periods varying from 5 to 11 days. The total amount administered varied from 1 to 2.2 cc. The gastric juice was prepared by the method already described; inactivation was accomplished by heating it to 100° C. for 15 minutes.

Group IV. Eighteen animals, 11 of which were treated and 7 of which served as untreated litter mate controls. All the experiments were carried out during 1940. The treated animals were given daily subcutaneous injections of an inactivated concentrated solution of liver extract (Lederle, 1 cc. containing 15 U.S.P. units), in doses varying from 0.1 to 0.2 cc., for periods varying from 2 to 10 days. The total amount administered varied from 0.4 to 1.5 cc. The liver extract was inactivated by heating it in the autoclave to 121.5° C. under 15 pounds of pressure for 30 minutes.

Group V. Eight animals, 5 of which were treated and 3 of which served as untreated litter mate controls. All the experiments were carried out during 1940. The treated animals were given 6 daily intraperitoneal injections of 0.2 cc. of concentrated gastric juice obtained from a patient with Addisonian pernicious anemia. The gastric juice was prepared by the method already described; neutralization with NaOH was unnecessary.

Blood was obtained from every immature animal in both treated and control groups at the beginning and the end of each experiment by cutting the tail vein, heparin being used as an anticoagulant. Only a few drops of blood were collected from each animal. The blood samples from the 6 adult male and 4 adult non-pregnant female opossums were secured by cardiac puncture.

The following determinations, the data from which were all analyzed statistically,[1] were carried out on each sample of blood:

1. Total number of red blood cells per c.mm., by the use of standardized pipettes.

2. Percentage of packed red blood cells in the whole blood, by the use of the Van Allen type of hematocrit and centrifugalization at 2400 revolutions per minute for 15 minutes.

3. Mean corpuscular volume, computed according to the method of Wintrobe.

4. Mean maximal diameter of the red blood cells. This value was obtained by measuring, at a magnification of 1000 times, from 100 to 200 red blood cells, which were stained with Wright's stain and focussed on a ground glass plate. Measurement of the mean maximal diameter of the red blood cells was obtained in all cases, but technical difficulties made some of the other determinations impossible, as indicated by Tables 1 to 5.

TABLE 1.—EFFECT OF NORMAL HUMAN GASTRIC JUICE ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP I).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	24	12	24	12
RBC in mill./c.mm.*	2.186	2.187	2.534	2.190
Variance of means	0.0012	0.0024	0.0045	0.0029
Difference	0.001		0.344	
t	0.0017		4.0070	
P	0.9		>0.01	
Number of animals	24	12	24	12
Volume of packed RBC,%*	34.67	35.20	29.06	33.95
Variance of means	0.2317	0.3542	0.6629	0.8608
Difference	0.53		4.89	
t	0.6925		3.9618	
P	0.5		>0.01	
Number of animals	24	12	24	12
Mean corpuscular volume of RBC in cubic microns*	158.75	161.75	114.75	156.33
Variance of means	9.0833	13.3121	5.8964	21.1455
Difference	3.0		41.58	
t	0.6339		7.9959	
P	0.5		>0.01	
Number of animals	25	14	25	14
Mean maximal diameter of RBC in microns*	8.988	9.157	7.920	8.828
Variance of means	0.0039	0.0093	0.0023	0.0040
Difference	0.169		0.908	
t	1.4698		11.4574	
P	0.2		>0.01	

* Average values. *RBC* = erythrocytes.

TABLE 2.—EFFECT OF CONCENTRATED LIVER EXTRACT ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP II).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	7	10	7	10
RBC in mill./c.mm.*	2.017	2.118	2.807	2.331
Variance of means	0.0060	0.0038	0.0019	0.0051
Difference	0.101		0.476	
t	1.0197		5.7056	
P	0.3		>0.01	
Number of animals	7	10	7	10
Volume of packed RBC, %*	32.29	34.10	33.09	35.47
Variance of means	0.8436	0.4918	2.3798	0.7809
Difference	1.81		2.38	
t	1.5662		1.3387	
P	0.1		0.2	
Number of animals	7	10	7	10
Mean corpuscular volume of RBC in cubic microns*	158.00	160.90	117.28	152.80
Variance of means	6.0952	12.6766	15.0028	37.7733
Difference	2.90		35.52	
t	0.6693		4.8893	
P	0.5		>0.01	
Number of animals	13	13	13	13
Mean maximal diameter of RBC in microns*	9.030	8.938	8.000	9.000
Variance of means	0.0081	0.0042	0.0189	0.0040
Difference	0.092		1.000	
t	0.9042		6.6111	
P	0.4		>0.01	

* Average values. *RBC* = erythrocytes.

TABLE 3.—EFFECT OF INACTIVATED NORMAL HUMAN GASTRIC JUICE ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP III).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	16	10	16	10
RBC in mill./c.mm.*	2.378	2.354	2.591	2.643
Variance of means	0.0045	0.0035	0.0043	0.0099
Difference	0.024		0.052	
t	0.2677		0.4336	
P	0.8		0.7	
Number of animals	16	10	16	10
*Volume of packed RBC,** %	33.28	33.10	31.31	31.50
Variance of means	0.2542	0.2989	0.8414	0.8611
Difference	0.18		0.19	
t	0.2420		0.1456	
P	0.8		0.9	
Number of animals	16	10	16	10
Mean corpuscular volume of RBC in cubic microns*	140.62	141.00	121.37	120.60
Variance of means	5.6875	3.6888	11.8416	30.8933
Difference	0.38		0.77	
t	0.0124		0.0117	
P	0.9		0.9	
Number of animals	16	10	16	10
Mean maximal diameter of RBC in microns*	8.27	8.29	8.08	8.09
Variance of means	0.0071	0.0096	0.0033	0.0017
Difference	0.02		0.01	
t	0.1546		0.1422	
P	0.9		0.9	

* Average values. *RBC* = erythrocytes.

TABLE 4.—EFFECT OF INACTIVATED CONCENTRATED LIVER EXTRACT ON ERYTHROCYTES FO POUCH OPOSSUMS (GROUP IV).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	10	7	10	7
RBC in mill./c.mm.*	2.347	2.394	2.355	2.701
Variance of means	0.0106	0.0107	0.0158	0.0059
Difference	0.047		0.346	
t	0.3221		2.3505	
P	0.7		0.05	
Number of animals	10	7	10	7
*Volume of packed RBC,** %	32.35	32.35	29.65	32.21
Variance of means	0.2781	0.2231	0.6059	0.0940
Difference	0		2.56	
t	..		3.0600	
P	..		>0.01	
Number of animals	10	7	10	7
Mean corpuscular volume of RBC in cubic microns*	139.10	136.14	127.70	119.85
Variance of means	57.0777	29.5714	18.5666	11.0714
Difference	2.96		7.85	
t	0.3223		1.4511	
P	0.3		0.2	
Number of animals	11	7	11	7
Mean maximal diameter of RBC in microns*	8.272	8.271	8.090	8.071
Variance of means	0.0050	0.0033	0.0021	0.0014
Difference	0.001		0.019	
t	0.0109		0.3376	
P	0.9		0.7	

* Average values. *RBC* = erythrocytes.

TABLE 5.—EFFECT OF CONCENTRATED HUMAN GASTRIC JUICE FROM A SUBJECT WITH ADDISONIAN PERNICIOUS ANEMIA ON ERYTHROCYTES OF POUCH OPOSSUMS (GROUP V).

Values.	Before treatment.		After treatment.	
	Experimental.	Control.	Experimental.	Control.
Number of animals	5	3	5	3
RBC in mill./c.mm.*	2.47	2.45	2.12	2.31
Volume of packed RBC, %*	35.10	33.67	28.80	28.33
Mean corpuscular volume of RBC in cubic microns*	143.6	137.6	136.2	122.3
Mean maximal diameter of RBC in microns*	8.70	8.73	8.62	8.46

* Average values. *RBC* = erythrocytes.

Results. At the beginning of the experiments the average total number of erythrocytes in the 117 immature pouch opossums was 2,265,000 per c.mm., as compared with 4,420,000 per c.mm. in the 10 adult animals. The average mean maximal diameter of the erythrocytes was 8.72 microns in the immature animals, as compared with 7.30 microns in the adult animals. The average mean corpuscular volume was 150 cubic microns in the immature animals, as compared with 87.99 cubic microns in the adult animals. Before treatment the bloods of the experimental animals and of their litter mate controls showed no significant differences in any of the values determined (Tables 1 to 5).

TABLE 6.—DISTRIBUTION OF ERYTHROCYTES ACCORDING TO DIAMETERS BEFORE AND AFTER TREATMENT.

	Number of animals.	Before treatment, cell diameters, %.			After treatment, cell diameters, %.		
		<8.5	8.5–9.5	>9.5	<8.5	8.5–9.5	>9.5
Concentrated Normal Human Gastric Juice.							
Experimental	20	22.00	63.45	14.50	72.10	24.92	2.97
Control	10	19.30	59.65	21.05	25.00	62.60	12.40
Concentrated Liver Extract.							
Experimental	9	23.61	61.70	14.68	62.61	32.37	5.00
Control	10	23.70	63.70	12.60	21.45	62.00	16.55
Inactivated Concentrated Normal Human Gastric Juice.							
Experimental	16	50.25	45.20	4.55	55.71	41.00	3.29
Control	11	44.33	49.66	6.00	60.66	37.08	2.25
Inactivated Concentrated Liver Extract.							
Experimental	11	49.33	47.66	3.00	60.06	37.80	2.13
Control	7	47.71	49.28	3.00	59.40	38.50	2.00
Concentrated Human Gastric Juice From Subject With Pernicious Anemia.							
Experimental	5	25.83	65.50	8.66	33.62	54.37	12.00
Control	3	25.33	67.66	7.00	39.40	47.80	12.80

The results of treatment in the various groups can be summarized as follows:

Group I. Effect of normal concentrated human gastric juice (Table 1): After treatment, in the experimental as compared to the control group, the mean number of red blood cells was significantly

increased and their mean packed volume, average mean corpuscular volume and average mean maximal diameter were significantly decreased. The decrease in the last three values was due to a relative increase in the number of smaller erythrocytes (Table 6), the change being graphically shown by a shift to the left of the Price-

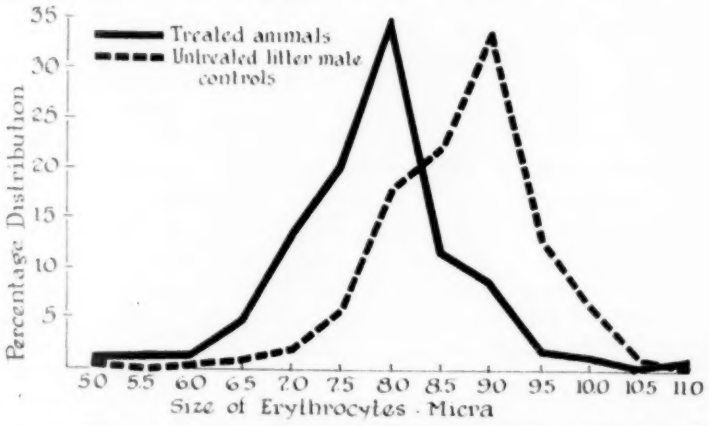

CHART 1.—Effect of normal concentrated human gastric juice on the percentage distribution, according to size, of the erythrocytes of pouch opossums.

Jones curve (Chart 1). The smaller erythrocytes showed a distribution of hemoglobin similar to that seen in mature red blood cells, thus differing from the uniformly hyperchromatic macrocytes of the fetal blood (Fig. 1).

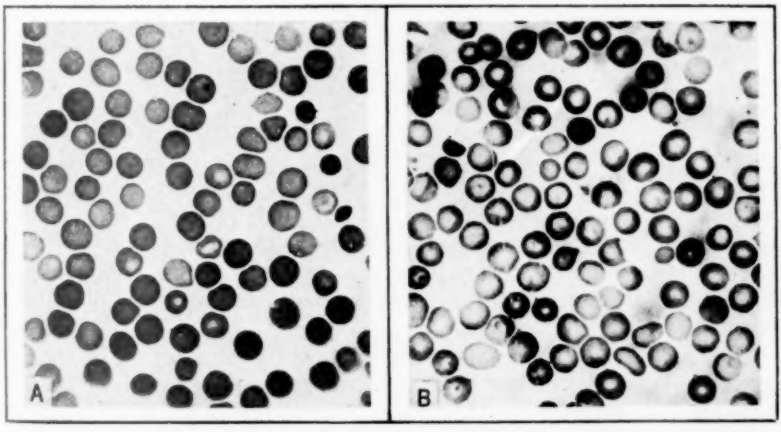

FIG. 1.—*A*, Erythrocytes of an untreated pouch opossum of 7.5 cm. crown-rump length. Hemoglobin tends to be evenly distributed throughout the cell. (Wright's stain, × 495.) *B*, Erythrocytes of a litter mate pouch opossum treated with normal concentrated human gastric juice for 4 days (0.8 cc.). The hemoglobin tends to be distributed toward the periphery of the cell. (Wright's stain, × 495.)

Group II. Effect of concentrated solution of liver extract (Table 2): After treatment, in the experimental as compared to the control groups, the mean number of red blood cells was significantly increased and their average mean corpuscular volume and average mean maximal diameter were significantly decreased. There was no significant change in the mean volume of the packed red blood cells. The decrease in the average mean values for the corpuscular volume and maximal diameter of the cells was due (Table 6) to a relative increase in the number of smaller erythrocytes, the change being graphically shown by a shift to the left of the Price-Jones curve (Chart 2). The smaller erythrocytes, as in Group I, showed a distribution of hemoglobin similar to that seen in mature red blood cells.

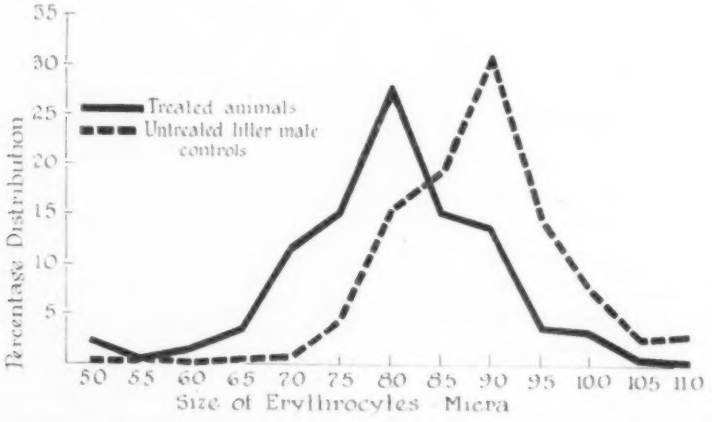

CHART 2.—Effect of concentrated liver extract solution (Lederle) on the percentage distribution, according to size, of the erythrocytes of pouch opossums.

Group III. Effect of inactivated concentrated normal human gastric juice (Table 3): After treatment, in the experimental as compared to the control group, there was no significant change in any of the values determined. The cell distribution according to diameters (Table 6) was essentially the same at the end of the experiment in both groups, and the hemoglobin was uniformly distributed throughout the cytoplasm of the erythrocytes of both control and treated animals.

Group IV. Effect of inactivated concentrated solution of liver extract (Table 4): After treatment, in the experimental as compared to the control group, there was a suggestive but not significant reduction in the mean number of red blood cells and a significant reduction in the mean volume of these packed cells. The other values were not significantly changed. The cell distribution according to diameters, as in Group III, was essentially the same

at the end of the experiment in both treated and control groups (Table 6), and the hemoglobin was uniformly distributed throughout the cytoplasm in all the animals.

Group V. Effect of administration of concentrated human gastric juice from a patient with Addisonian pernicious anemia (Table 5): After treatment there were no significant differences between the erythrocytes of the control and experimental groups, and the cell distribution according to diameters was essentially the same in both groups. Because of the small number of animals used the results of the statistical analyses of these data are not included in Table 5.

In the experiments reported in Groups III, IV, and V, all of which were performed in 1940, the immature opossums found in the pouches were somewhat larger than those found in 1939. As a result, the number of red blood cells per c.mm. was somewhat greater and the average mean corpuscular volume and average mean maximal diameter were somewhat less at the beginning of the experiments than these respective values for the animals studied in 1939 (Tables 1 to 5).

Inactivated gastric juice was slightly toxic for the experimental animals, as indicated by their general appearance compared to that of their untreated litter mate controls, and by the death of several of the animals. The same observation was made concerning the inactivated concentrated liver extract used in Group IV and the gastric juice from the patient with Addisonian pernicious anemia used in Group V, although in the latter experiment none of the animals died.

Comment. Our comparative studies of untreated adult opossums and untreated immature pouch opossums showed differences between the erythrocytes of the two groups. The young animals, as compared with the adult animals, showed an anemia and also showed a relative macrocytosis, as indicated by the larger mean corpuscular volume and the greater mean maximal diameter of the red blood cells. Morphologically, the hemoglobin of the majority of the erythrocytes of the immature animals was distributed evenly throughout the cells, whereas in the adults it was usually more concentrated at the periphery of the cells and the central zones were relatively clear. As the young animals matured, the anemia improved and the number of macrocytes decreased until eventually the red blood cells resembled those of the adult animals in both numbers and appearance.

Studies of the action of normal human gastric juice and of concentrated liver extract solution showed that after the administration of these substances the average number of red blood cells was relatively increased and their average size was relatively decreased. As has been pointed out, the diminution in the average size of the erythrocytes was caused by an increase in the number of smaller

cells, which morphologically resembled the erythrocytes found in the adult animals. As these smaller cells increased in numbers, the blood pictures of the treated animals approached those of the adult animals, although in no instance did they become identical with them.

Normal human gastric juice and concentrated liver extract solution altered to approximately the same degree all the values determined except the mean packed volume of red blood cells. This value was significantly reduced by the administration of gastric juice, but was not significantly altered by the liver extract solution. Such findings suggest that the gastric juice reduced the size of the erythrocytes proportionately more than it increased the number, whereas the concentrated liver extract affected both values proportionately (Tables 1 and 2).

According to these experiments, when the thermolabile factor in human gastric juice was destroyed by heating, the maturation of the red blood cells in the mammalian fetus was not accelerated (Table 3). A similar observation was made when the antianemic principles in concentrated liver extract were destroyed by heating (Table 4). Injections of the inactivated extract, furthermore, not only failed to accelerate normal maturation of the cells, but may actually have influenced it adversely. During the course of the experiment (Table 4) the mean number of erythrocytes in the control group somewhat increased, but the mean number in the experimental group remained at essentially the same level, which suggests that the inactivated liver extract solution may have inhibited the normal increase in number. On the other hand, although the inactivated liver extract solution apparently suppressed the number of red blood cells, it had no effect upon the average mean maximal diameter of these cells in the experimental as compared to the control groups (Table 4). At the end of the experiment there was therefore a significant reduction in the packed volume of the red blood cells in the treated as compared to the untreated animals. This apparent inhibition of normal maturation suggests that toxic elements were formed in the liver extract solution as a result of heating.

It is important to note again that the animals used for testing inactivated human gastric juice and inactivated concentrated liver extract solution showed greater variations in size than those used for testing the active principles, and were somewhat larger. As a result, the number of erythrocytes was somewhat greater and the size of these cells somewhat smaller at the beginning of the experiments with inactivated principles than at the beginning of the experiments with active antianemic principles. It is possible that the variations in size of the animals may account for some of the irregularities in the numerical data in the experiments with inactivated materials. We are inclined to believe that the size (age) of

the animals has considerable bearing on the results, and that opossums with uniform crown-rump lengths of 5 to 6 cm., with erythrocytes measuring as near 9 microns in diameter as possible, are optimum for such studies. It would be advantageous if future studies were carried out on the basis of these criteria.

The number of animals which received gastric juice from a patient with Addisonian pernicious anemia was too small to permit definite conclusions as to the action of this substance, and the experiments should be repeated with a larger series. The data suggest, however, that gastric juice secured from this source not only failed to accelerate the development of the erythrocytes but also may have slightly retarded their maturation.

These studies show that the red blood cells of the immature opossum are constantly larger than those of adults of the same species. As the pouch animals normally mature, the erythrocytes become smaller and eventually approximate in numbers, size and appearance those found in adult animals. Similarly, the erythrocytes of patients with pernicious anemia are relatively larger during relapses of the disease, whereas remissions are always associated with a reduction in the size and a change in the appearance of these cells. These similarities suggest that in the developing opossums the principles required for the complete maturation of the red blood cells may be lacking, just as they have been shown to be lacking in patients with pernicious anemia. As the animals mature in the maternal pouch, the necessary principles presumably become available and the signs of deficiency, as reflected in the blood picture, therefore gradually disappear. This hypothesis is substantiated by the observation that the experimental administration of antianemic principles to immature opossums significantly alters the character of their red blood cells.

Summary. 1. Studies on immature developing opossums, living in the maternal pouch, showed a macrocytic anemia in these animals as compared with adult animals of the same species. As the young animals matured, the character of their red blood cells gradually changed until it assumed that of adult animals.

2. The direct injection of either concentrated normal human gastric juice or of a concentrated solution of liver extract significantly reduced the mean maximal diameter and the mean corpuscular volume of the erythrocytes, and significantly increased their number, in the treated pouch opossums as compared with their untreated litter mate controls. These changes were effected through a relative increase in the number of smaller erythrocytes.

3. The direct injection of inactivated normal human gastric juice, of inactivated concentrated liver extract solution, and of gastric juice from a patient with Addisonian pernicious anemia failed to increase significantly the number of red blood cells or to reduce significantly the mean maximal diameter and the mean

corpuscular volume of these cells in the treated pouch opossums as compared to their untreated litter mate controls.

ADDENDUM. After this paper was submitted for publication, there appeared a review by O. P. Jones: Transmission of the Antianemic Principles Across the Placenta and Its Influence on Embryonic Erythropoiesis (Arch. Int. Med., **68**, 476, 1941), in which he cites our preliminary report (Proc. Soc. Exp. Biol. and Med., **42**, 544, 1939) and remarks in a footnote that the diameters of only the largest red blood cells were measured in our studies. This interpretation of our method of measuring cell diameters is incorrect and may have arisen from our use of the term "mean maximal diameter." In our work there was no selection of cells. On each blood smear, every cell was measured in turn until 100 or 200 cells had been encountered. Because the cell outlines did not always form perfect circles, however, the greatest —or maximal—diameter of each cell was selected for measurement.

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SYPHILITIC AORTIC INSUFFICIENCY: THE ASYMPTOMATIC PHASE.*

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DURATION of life, after the onset of symptoms due to syphilis of the aortic valve, is generally stated to be relatively short.[1,3,11,15,21] The picture described in the standard texts is one of the rapid developments of symptoms and signs of cardiac insufficiency in a patient in the forties or fifties who had previously been perfectly active and well.[1,3,11,15,21] It is generally agreed among the various authorities that survival from this stage on is usually a matter of only 1 or 2 years. It is recognized[12] that the use of specific antisyphilitic therapy in aortic syphilis will prolong life, even doubling the average expectancy, but the emphasis in practically all authoritative works

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is on the clinical course after the onset of failure with but passing reference to the course before failure appears.

Yet in the study of 1000 cardiacs, 10 years after the original examination, Grant[5] has shown that the 10-year mortality associated with syphilis of the aortic valve is only 64%, actually less than the mortality rate over the same period of patients with mitral stenosis with auricular fibrillation (68%).

This discrepancy between the poor prognosis usually accorded patients with syphilitic aortic regurgitation after the onset of symptoms, and the 10-year statistics of Grant, is a reflection of the differences between two types of clinical material. Grant's patients were all ambulatory men who were either in, or being considered for military service. Relatively few of these men would have had examinations of their hearts at that time under normal conditions. The aortic syphilis seen by most internists is not selected from large groups of ambulatory patients with syphilis, but is seen in individuals who have sought medical care because of symptoms of cardiac insufficiency. This suggests that aortic insufficiency due to syphilis is actually present in a clinically recognizable form for a relatively lengthy period of time before the development of symptoms, but that because of this asymptomatic state the patients do not seek medical care and hence are not discovered. Obviously the only way patients with this asymptomatic form of valvular syphilis can be discovered is by doing routine physical examinations on all known syphilitics.

During the 4½-year period from October, 1936, to April, 1941, 2718 syphilitic patients were examined in the syphilis clinic of this hospital, and 100 (3.6%) were found to have syphilitic aortic insufficiency. Nine of these had aneurysms as well, leaving 91 (3.3%) patients with the valvular defect alone. The diagnosis in every case was confirmed by two or more observers. Our criterion was the repeatedly demonstrable presence of a diastolic murmur over the aortic area or down the left sternal border in a patient known to have been infected with syphilis and who had no evidence of mitral stenosis or congenital heart disease either clinically or by Roentgen ray.

The patients were all examined on numerous occasions. It is frequently observed that a murmur, difficult to detect or inaudible with the patient in the recumbent position, can be brought out by having the patient sit up, lean forward and expire forcibly. The precordium is then examined while the patient holds his breath in full expiration.

During this period we were soon impressed by the fact that the presenting clinical picture and subsequent course of the disease in the majority of these patients differed sharply from that of the classical descriptions, particularly in respect to their ability to do work without symptoms or signs of cardiac insufficiency. Accord-

ingly, a clinical study of all of our patients with syphilitic aortic insufficiency without aneurysm has been made to obtain information on this asymptomatic phase of the disease.

Of the 91 patients with aortic valvular syphilis, 45 (49%), or nearly one-half of the group, had no symptoms of cardiac insufficiency at the time of the original diagnosis. An additional 13 (14%) admitted symptoms only after specific questioning but had not sought medical care because of these symptoms; and 33 (36%) patients had definite symptoms related to their aortic disease. On this basis of the clinical impression of the status of the individual patient at the time of diagnosis three groups were formed: Group I (asymptomatic), Group II (symptoms on questioning only); and Group III (symptomatic).

By asymptomatic is meant that all of these patients denied any exertional dyspnea, orthopnea, substernal pain on effort or at rest, palpitation or ankle edema. The majority were working and all of them were completely unaware of the fact that they had heart disease. The patients in the symptomatic group (Group III) presented the picture more generally regarded as typical of syphilitic aortic regurgitation. The presenting complaint in each case was directly referable to the cardiovascular system, and in many, angina of effort and symptoms suggesting failure were present.

TABLE 1.—PATIENTS FOLLOWED MORE THAN 2 YEARS.

Group.	No. of patients	Dead.		Living but have developed symptoms.
		Died of heart disease.	Died of other cause.	
I (Asymptomatic)	20	1	1	1
II (Symptoms on questioning only)	8	1	0	0
III (Symptomatic)	15	1	1	
Total	43	3	2	

Period of Observation. Twenty patients, or almost one-half of the asymptomatic group (Group I), have been followed for more than 2 years (Table 1). Two of these 20 have died, both 2½ years after the diagnosis, one of his heart disease and the other of a carcinoma of the bladder. Two patients of the 25 who have been followed for less than 2 years have died, one of a gastric carcinoma and the other of paresis (Table 2). Two patients of this entire Group I have developed symptoms under observation. One developed slight exertional dyspnea 3 months after the diagnosis was made and angina of effort 4 months later. The other patient who has been followed for more than 7 years has developed slight dyspnea on climbing to his fourth floor room within the past year. However, he has such marked loss of vision that he is forced to proceed much more slowly than normal so that it is highly probable that he would have more marked symptoms if he were able to be more active.

Eight of the 13 patients in Group II (symptoms on questioning only) have been followed for more than 2 years. One of this group died 3½ years after the diagnosis, presumably because of heart disease.

Fifteen of the 33 patients in Group III (symptomatic) have been followed for more than 2 years. Eight of the entire group have died, 2 of carcinoma and the others as a result of their heart disease.

Thus, of the entire group of 91 patients with aortic valvular syphilis, 43 (46%), or almost one-half, have been followed for more than 2 years. The follow-up by years is recorded in Table 3.

TABLE 2.—PATIENTS FOLLOWED LESS THAN 2 YEARS.

Group.	No. of patients.	Dead.		Living but have developed symptoms.
		Died of heart disease.	Died of other cause.	
I (Asymptomatic)	25	0	2	1
II (Symptoms on questioning only)	5	0	0	1
III (Symptomatic)	18	5	1	
Total	48	5	3	

TABLE 3.—PERIOD OF OBSERVATION OF 91 PATIENTS WITH SYPHILITIC AORTIC INSUFFICIENCY.

Years of observation.*	Number of patients.		
	Group I.	Group II.	Group III.
Less than 1	14	2	11 (5 deaths)
1– 2	11	3	7 (1 death)
2– 3	8	2	8 (1 death)
3– 4	5	5	1
4– 5	2	1	3 (1 death)
5– 6	0	..	1
6– 7	1	..	2
7– 8	2		
8– 9	0		
9–10	2		
	45 (4 deaths)	13 (1 death)	33 (8 deaths)

* Records were available of some of these patients who had been under observation in this institution before this clinic was started.

Any symptomatic classification of cardiac patients based solely on the history and physical examination has certain obvious sources of error. The most prominent of these is the variation in the ability of the patient to describe symptoms accurately and in the interpretation of the patient's statements by the examiner. In order to obtain data which could be weighed objectively to evaluate the patients classified as asymptomatic, studies of the circulation were performed. By examining the records and questioning these patients, we have attempted to find out the type and amount of work they are actually doing at present and what brought them to seek medical care.

Analysis of Presenting Complaints. Not one of the 45 patients in the asymptomatic group sought medical care because of symptoms relating to the cardiovascular system. Of the 13 patients in Group II there was also none whose cardiac symptoms influenced him to seek medical care. As would be expected the patients in Group III sought medical care because of symptoms of cardiac insufficiency in practically all instances. However, even in this group there were 2 patients whose syphilis, and consequently whose cardiac disease, was first detected by the obtaining of a blood Wassermann as a routine measure, 1 of these being the father of a patient with juvenile paresis discovered in a family investigation. In the cases of the other 31, cardiac symptoms brought them to the doctors and the clinical diagnosis of aortic syphilis was the cause of their being referred to the syphilis clinic.

Combining the three groups of 91 patients with syphilitic aortic insufficiency, only 31 (34%) sought medical care because of symptoms referable to the heart; 53 (58%) consulted physicians or came to the hospital because of complaints entirely unrelated to the cardiovascular system; and 7 (8%) did not seek medical care at all but were discovered to have syphilis by the routine testing of donors, families of known syphilitics, and applicants for employment. The presenting complaint or disease causing the complaint for each member of Groups I and II are listed in Table 4.

TABLE 4.—COMPLAINTS OR PATHOLOGIC CONDITION RESPONSIBLE FOR THE COMPLAINTS WHICH BROUGHT PATIENTS IN GROUPS I AND II TO SEEK MEDICAL CARE.

Presenting complaint or cause of complaint.	Number of patients.	
	Group I (asymptomatic).	Group II (symptoms on questioning only).
Headaches and nervousness	4	0
Arthritis	3	1
Tabetic pains	3	0
Peptic ulcer	3	2
Uterine bleeding	3	0
Dizziness	0	2
Voluntary donor	2	0
Miscellaneous*	27	7

* The following were presenting symptoms in 1 case each: (Group I) Upper respiratory infection, trichiniasis, nausea, skin rash, failing vision, attacks of unconsciousness, bronchiectasis, Malta fever, fractured vertebræ, infected finger, hernia repair, renal colic, urethral discharge, carcinoma of bladder, epididymitis, prostatic hypertrophy, pyelitis, renal tuberculosis, vaginal discharge, menopausal syndrome, uterine fibroid, tinnitus and deafness, cataract, preëmployment examination, family investigation, routine serology by private physician and by Life Extension Institute; (Group II) Failing vision, unconsciousness, lobar pneumonia, cholelithiasis, gastritis, fractured tibia, routine serology in jail.

Of the entire group of 91 with syphilitic aortic regurgitation, 47 patients were available for clinical investigation. Twenty-three patients were from Group I, 7 from Group II, and 17 from Group III. It must be emphasized that the classification of the individual

patients into the various groups was done solely on the basis of the examiner's judgment at the time of the initial examination in the clinic. Some changes in the status of individual patients have occurred since their original classification, but these have been few, so that in general the circulatory studies serve as an objective check on the classification.

Data on the amount of work that the patients are actually doing are included only for this group of 47 who were the subjects of the clinical studies as it was felt that, in this particular, only the most recent information would be of any value.

Sixteen of the 23 (Group I) patients have jobs at present. An additional 4 are housewives who do all their own housework, and the remaining 3 are men who are unable to secure employment. None of these patients has modified his activity in any way, either at work or at home, because of his cardiac disease.

Two of the 7 patients studied in Group II are gainfully employed, 1 is able to work but cannot find a job. An additional 2 are housewives who do all their own work. One is unable to work because of central nervous system syphilis, and 1 because of a chronic osteomyelitis.

In Group III there are 3 patients who are employed, an additional 2 who do all their own housework, 4 who help with housework but whose activity is modified because of the heart disease, and 8 who are unable to do any work at all because of cardiac symptoms. The type and hours of work are recorded in Table 5.

Measurements of the Circulation. Measurements of the vital capacity, arm-to-tongue circulation time and venous pressure were obtained on the 47 patients in the three groups.

Decholin was used for the arm-to-tongue circulation time. Five cubic centimeters of a 20% solution were injected rapidly through an 18-gauge needle into an antecubital vein while the individual was lying quietly in the supine position. The time was recorded from the beginning of the injection until the first perception of the bitter taste by the patient. All tests were repeated within 2 minutes as a check. The value recorded is an average of the two readings. In a few instances when an antecubital vein was not available, more distal arm veins were entered with a smaller needle (20-gauge). In every one of these cases, however, the circulation time was well within normal limits. Tarr and his associates[19] found that the normal value for the circulation time by this method ranged between 10 and 16 seconds. Stewart and Watson[17] found that the individual estimations in a group of normal subjects tested by this method ranged from 10.4 to 17 seconds. The venous pressure was measured by the direct method, using an antecubital vein placed on a level with the right auricle. An L-shaped glass tube attached to a 3-way stopcock, syringe and an 18-gauge needle were used. The apparatus was filled with sterile normal saline solution before the veni-

puncture and the direct pressure readings recorded. Normal values for this method are up to 120 mm. saline. Measurements on a 2-meter Roentgen ray film of the greatest transverse cardiac diameter, the internal thoracic diameter just above the diaphragm, and calculations of the cardiothoracic ratio were made. The vital capacity was measured in the usual fashion with the subject in a sitting position, recorded in cubic centimeters and calculated in per cent of normal. Normal values were taken from those of West,[20] namely 2.5 liters per square meter of surface area for men and 2 liters per square meter for women.

TABLE 5.—TYPE AND APPROXIMATE HOURS OF WORK PERFORMED BY THE 45 PATIENTS STUDIED.

	Type of work.	Hours (per day).
	Group I—(Asymptomatic).	
J. Mc.	Distributor for bottled gas company	9
B. F.	Head matron, department store	8
J. F.	Apartment house superintendent	9
M. F.	Cook	8
M. G.	Waiter	8
S. K.	Janitor for 44-family building	15
C. K.	Machine shop	8
J. M.	Chauffeur	10–16
A. R.	Furrier	10
M. V.	Cabinet maker	12–16
M. D.	Taxi driver	10
B. A.	Cigar maker (2 days a week; also does own housework)	10
S. M.	Seamstress (also helps with housework)	6
M. Z.	Salesman	5–6
B. J.	Nursemaid (2 children)	Full time
H. J.	Nursemaid (4 children)	Full time
B. F.	Housewife—housework for 6 people	Full time
B. G.	Housewife—housework for 2 people	
C. M.	Housewife—housework for 2 people	
A. K.	Housewife—housework for 2 people	
J. E.	Unemployed—able to work	
A. W.	Unemployed—able to work	
A. I.	Domestic servant	Full time
	Group II—(Symptoms on Questioning Only).	
L. L.	Waiter	6
H. J.	Decorator	7
G. F.	Housewife—housework for 2	
F. W.	Housewife—housework for 2	
F. K.	Unemployed—able to work	
J. B.	Unemployed—unable to work because of CNS syphilis	
J. Mc.	Unemployed—unable to work because of osteomyelitis	
	*Group III—(Symptomatic).**	
W. W.	Bricklayer (3 days a week)	8
S. W.	Salesman (4 days a week)	8
M. B.	Bar tender (1 day a week)	9
M. M.	Housework for 2 people	
R. K.	Housework for 3 people	

* Of the remaining 12 Group III patients, 4 are able to assist with housework but cannot work all day, and 8 are unable to work at all.

Data. The data for the patients of all three groups are recorded in Table 6. The correlation between the clinical impression of the state of the circulation and the data obtained from these tests was

quite close. Closest correlation was found, as would be expected, in the circulation times and cardiothoracic ratios. The vital capacity readings can be said to show only a general relationship to the presence or absence of symptoms. This is in accord with the observations of Harrison.[7]

TABLE 6.

Name.	Circ. time, sec.	Venous pressure, mm. saline.	Vital capacity. Cc.	Vital capacity. % of normal.	Cardiothoracic ratio.	Heart width, cm.	Aortic dilatation.*	Blood pressure.
Group I (Asymptomatic).								
B. J.	10.2	79	2350	78	42	11.2	0	150/85
M. F.	10.6	70	2400	74	46	13	0	150/82
J. F.	10.7	60	2000	74	46	10.2	0	160/80
S. M.	11.4	..	2700	90	46	12	0	140/80
M. I.	11.9	81	2300	66	50	13	+	130/90
E. G.	12.0	100	2300	80	43	12.4	0	150/70
H. J.	12.1	50	2000	74	69	16	0	170/90
J. M.	12.5	70	3800	90	..	..	0	180/90
A. R.	12.6	100	3400	72	..	..	..	138/96
B. F.	13.9	95	2000	66	56	13.5	+	270/145
A. K.	14	..	2000	66	53	12.9	0	155/80
B. A.	14	90	2800	80	49	15.5	+	190/54
M. D.	14.5	94	3500	80	42	11.5	0	130/60
A. W.	15	92	3150	85	46	14.5	+	168/64
M. Z.	15.8	115	2500	60	..	..	0	190/80
H. M.	16.6	80	2400	56	..	..	..	210/70
D. F.	16.9	44	1900	54	55	15	0	190/90
M. V.	17.2	68	2900	62	49	14	0	125/60
S. K.	17.3	88	3400	94	52	14.5	0	140/70
S. E.	18.1	51	3350	80	42	11	+	170/90
M. Mc.	18.4	88	1400	38	55	15	+	162/82
M. G.	18.5	70	2200	55	54	13.9	0	180/90
C. K.	..	90	3500	80	42	15.5	+	158/80
Group II (Symptoms on Questioning Only).								
F. K.	12.2	103	3600	84	58	16.2	0	170/70
G. F.	12.7	..	2000	70	43	10.4	+	188/86
H. J.	13.6	37	2500	75	49	12	0	135/60
F. W.	14.4	78	1600	45	58	17	+	214/78
L. L.	15.6	50	2700	78	47	13.3	0	208/80
J. B.	22.4	65	3100	76	50	16	0	170/65
J. Mc.	29.8	135	1850	42	67	17.5	+	200/65
Group III (Symptomatic).								
S. W.	12.6	90	2200	46	49	14.7	+	140/50
W. W.	13	54	3800	83	43	13.5	0	150/55
G. E.	13.7	124	2000	61	53	14	0	190/94
R. K.	14.1	102	2700	90	42	10.5	0	180/90
C. B.	14.5	98	2000	45	51	14	0	190/70
J. G.	14.7	85	2800	63	55	16	0	160/60
A. C.	14.9	82	2300	81	55	13.2	+	180/60
A. N.	16.3	99	1750	58	55	13.5	0	212/110
M. B.	16.6	97	2600	53	53	17	+	145/60
M. Mc.	17.9	130	2000	76	58	14.8	+	158/32
G. L.	19.7	86	2700	72	55	15.4	+	150/40
G. W.	22.5	50	2000	70	60	13.3	0	170/45
J. K.	22.8	117	2500	56	..	..	..	165/50
J. Mc.	23.8	82	2400	59	68	19	+	220/90
J. P.	24.6	72	2500	64	57	17.3	0	194/50
F. N.	28.2	52	2000	41	56	16.8	+	140/70
J. M.	29.8	53	3000	65	57	18.2	+	170/15

* By Roentgen ray.

There were only 5 patients of the 23 in the asymptomatic group who had circulation times higher than 17 seconds, and the extreme was 18.5 seconds. The venous pressure determinations were all within normal limits, ranging from 44 to 115 mm. of saline. In 7 patients the cardiothoracic ratio, calculated from the measurements of the Roentgen ray, was more than 50 with an extreme of 69.

In Group II, of 7 patients studied the circulation time was normal in 5, markedly prolonged in 2. One of these 2 patients has paresis and cannot be relied upon regarding symptoms. The other patient is a cripple because of a chronic osteomyelitis of the tibia and would probably have symptoms if he were capable of any very great activity. The venous pressure determinations were normal in all except the latter patient mentioned above. The cardiothoracic ratio was increased in 3 of the 7.

Of the 17 patients in Group III, there were 8 with prolongation of the circulation time, 2 with increased venous pressure and 13 with a cardiothoracic ratio of greater than 50. It is noteworthy that of the patients in this group in the greatest degree of failure, none had increased venous pressure. These patients were all receiving digitalis. There were only 2 patients in this group (W. W. and S. W.) who showed normal values for all three examinations. Both of these would be classified as completely asymptomatic on the basis of their present status but are included in Group III because their original complaints were cardiac. One (S. W.), following therapeutic malaria in 1934, developed congestive failure which disappeared promptly and has not returned. He is working as a bricklayer at present. The other (W. W.) originally sought medical care because of attacks of substernal pain unrelated to exertion which completely disappeared following antisyphilitic therapy. He is working as a salesman at present.

Combining the data for all three groups: of 47 patients there were 15 with abnormally prolonged circulation times, 3 with increased venous pressure, and 23 with a cardiothoracic ratio of more than 50.

Roentgenologic Evidence of Aortic Dilatation. There is a great variety of opinion as to the significance of the presence or absence of aortic widening as demonstrated by Roentgen ray in the diagnosis of aortic syphilis.[6, 8, 16, 18] No universally accepted method of measuring the aorta is available.[18] The subjective element in estimations by fluoroscopy is a great variable, and as has been recently emphasized[13] the part of the aorta most frequently involved by syphilis, the root, is not visible for the first 1.5 to 2 cm. on plates taken by conventional techniques. Because these pitfalls exist in the use of the Roentgen ray or fluoroscope as an aid to establishing the presence of syphilis in the aorta, it is of interest to see what the roentgenologic findings are in this group in whom the presence of aortic syphilis is known.

Estimations of aortic width of these patients were made on the basis of left oblique and P–A plates supplemented in the majority of instances by fluoroscopy. Eighty-seven of the 91 patients with aortic regurgitation were examined by these methods. The aortas were considered to be widened in 50 (57%) of these and in 37 (43%) there was no evidence of aortic dilatation.

Wassermann Reactions. Because there is such a wide range (65% to 95%) in the reported incidence of positive Wassermann reactions in patients with syphilitic aortic insufficiency,[4,9,14,24] we have included our data for the entire 91 patients.

The blood Wassermann reaction was positive in 78 (85%) patients. In 8 other patients (9%) the reaction was doubtful or negative but there was a history of a previous positive test and previous antisyphilitic therapy. In 4 patients (4.3%) the Wassermann reaction was doubtful (1+ to 3+) with no history of previously positive tests (2 of these patients showed positive (4+) Kline and Kahn flocculation tests). One patient had a negative blood Wassermann but the spinal fluid Wassermann reaction was positive. Thus, in every one of the 91 patients there was definite serologic evidence of syphilis or a history of such evidence.

These patients represent a group, a majority of whom would not have been known to have aortic syphilis had not the presence of the syphilis been discovered first, either by routine testing or because of clinical evidence of neurosyphilis. Therefore, there is a possible source of error in estimating the incidence of positive serologic reactions in such material. For comparison, data on this point were obtained in another group of patients, namely from the records of all patients admitted to the in-patient service of this hospital since September 1, 1932, in whom a clinical or postmortem diagnosis of aortic valvular syphilis had been made. All patients in the clinic series reviewed above are excluded from this group. These patients, therefore, were not examined simply because they were known to have syphilis. The serologic data were obtained from the routine serologies taken on all patients admitted to the in-patient service.

Of a total of 44 cases, 32 had positive (4+) blood Wassermann reactions, 6 had doubtful (1+ to 3+) reactions but gave a history of having had a previous positive reaction with treatment, and 1 had an anticomplementary reaction but had a positive spinal fluid Wassermann. In 2 patients, a doubtful reaction (1+ to 3+) in the absence of any history was obtained and in 3 others (6%) there was no serologic or collateral evidence of syphilis other than the presumably insignificant finding of doubtful (1+ to 3+) Kline flocculation tests.

These three groups of patients combined (135) represent all the patients with syphilitic aortic insufficiency uncomplicated by aneurysm, seen in any department of this hospital during the 8½-year period from September 1, 1932, to April 1, 1941. Thus, there were

only 3 patients (2%) of the entire 135 who showed neither serologic nor historical evidence of syphilis.

TABLE 7.—INCIDENCE OF POSITIVE WASSERMANN REACTIONS IN 135 PATIENTS WITH SYPHILITIC AORTIC REGURGITATION.

	No. of patients.	Per cent.
Total	135	
Positive blood Wassermanns	110	81.5
Doubtful (1+–3+) blood Wassermanns but history of previous positive Wassermann and therapy	14	10.4
Negative blood Wassermann but positive spinal fluid Wassermann	2	1.5
Doubtful (1+–3+) blood Wassermann with no history of previous positive or therapy	6	4.4
Negative Wassermann, no history of previous positive Wassermann or of therapy	3	2.2

Discussion. Examination of this material shows that the usually accepted clinical concept of syphilitic aortic insufficiency represents only the end stage of the condition. There is a clinically recognizable stage which may be reckoned in terms of years during which the patient has no symptoms referable to the heart and is able to carry on normal activity. That such a stage exists is, of course, well known. However, it has seemed to us that the fact has never been sufficiently emphasized that in a large group of syphilitics, asymptomatic aortic valvular disease is actually more common than the symptomatic form. Obviously patients in this phase of the disease would not be seen in any numbers in in-patient services or cardiac clinics as they are completely unaware of their need for medical care. The list of chief complaints of the 58 patients in Groups I and II shows a great variety of symptoms none of which would serve to direct attention to the heart. For many of these complaints the patients would be handled in special clinics in which an examination of the heart is not done routinely. It is only by the examination of all known syphilitics and the unearthing of previously unknown symptomless syphilis by routine serologic testing that patients with aortic regurgitation in the asymptomatic phase will be discovered. With the recent greatly increased use of routine serologic testing as a case-finding method, many more syphilitics who did not realize the fact of their infection are being found so that the recognition of this type of valvular syphilis is becoming more important.

Prognostic data, based as they are on the course following the onset of symptoms of failure, are valueless in this type of case. The information to be sought is how long these patients survive from the time the valvular disease is first detectable.

As there is an increasing body of evidence that specific antisyphilitic therapy, including the judicious use of arsenicals, prolongs life in cardiovascular syphilis, the recognition of this asymptomatic

phase of aortic valvular syphilis is of therapeutic value. For, although the active syphilitic process of the aorta is predominantly in the media and the vasa vasorum of the adventitia, the ultimate anatomic change causing the altered physiologic response is in the intima and the valve leaflets. In a recent publication on this subject, Wilens[23] has stated, "Thus the weight of evidence seems to indicate that the cusps are secondarily and passively altered in much the same fashion as is the intima elsewhere. Primary specific inflammatory changes of syphilitic aortitis involving the intima directly are perhaps just as rare as similar changes in the leaflets of the aortic valve, the superior portions of which, at least, are but appendages of the inner layer of the aorta." As these all-important intimal and valvular changes are largely non-inflammatory, they are presumably unaffected by therapy. The rôle of specific therapy here is to check the gummatous process in the underlying aorta before the passive alterations of the valve have become too far advanced. There is, of course, no exact clinical method for measuring how far the underlying aortitis has progressed. However, it is reasonable to assume that these asymptomatic patients with the early diastolic murmurs have a less advanced stage of the inflammatory process in the aortic wall and hence can receive maximum benefit from specific therapy.

With but few exceptions the living patients in all three groups are receiving continuous antisyphilitic therapy, including courses of neoarsphenamine administered cautiously. The period of follow-up is too short to attempt to evaluate the effects of the therapy at this time. We can say, however, that we have seen none of the reported harmful effects of therapy such as the therapeutic paradox or Herxheimer reactions around the coronary ostia.[11,22]

The circulatory studies in most instances conformed closely to the clinical evaluation of the status of the individual patients. The measurements served as collateral evidence of the good functional capacity of the circulation of the members of the asymptomatic group. As would be expected the earliest objective change after the development of the diastolic murmur was the alteration of the cardiothoracic ratio. The fact that the aortas of the 37 (43%) of a total of 87 patients with syphilitic aortic regurgitation were considered to be normal in width by Roentgen ray and fluoroscopy emphasizes the inadequacy of the Roentgen ray as a means of excluding the presence of aortic syphilis. In making the decision between treating or not treating a middle-aged patient with apparently latent syphilis, too great reliance should not be placed on the normal appearance of the aorta by Roentgen ray. This fact alone serves as a justification for the policy of completely reëxamining all syphilitic patients at regular intervals.

Analysis of the specificity of the Wassermann reaction shows that in only 3 patients (2.2%) of a total of 135 with syphilitic aortic

insufficiency was the blood Wassermann reaction negative in the absence of a history of previous treatment for syphilis. The discrepancy between these figures and those quoted in the literature is partially due to the marked increase in the sensitivity of the Wassermann reaction since its introduction 34 years ago. Even now the sensitivity of the test varies between different laboratories depending upon the technique used.[10] While no exact figures are available in the literature, an estimate has been made that the test commonly employed during the decade 1910–1920 gave positive results in 70% to 80% of all patients with secondary syphilis,[2a] whereas with modern techniques the Wassermann reaction is almost 100% sensitive in syphilis of this type.[2b] Obviously, analyses of series of cases dating back to the twenties or earlier will give an erroneous impression as to the incidence of positive Wassermanns among cardiovascular syphilitics today.

Summary.—1. In a 4½-year period in the syphilis division of the medical clinics of the New York Hospital, the incidence of syphilitic aortic insufficiency without aneurysm was 3.4% (91 of 2718).

2. One-half of these patients (49.5%) with aortic regurgitation denied any symptoms of cardiac insufficiency at the time of diagnosis.

3. Only 31 (34%) of the 91 patients sought medical care because of symptoms referable to the heart, 53 (58%) sought care for noncardiac complaints, and 7 (8%) were brought under medical care by the routine serologic testing of supposedly well people.

4. Of 28 of these asymptomatic patients followed for more than 2 years, 2 have died of heart disease and only 2 have developed symptoms.

5. Circulatory studies (vital capacity, venous pressure, circulation time and roentgenoscopy) of 47 of these patients showed a close correlation with the clinical impression of their cardiac status.

6. The aortic width, as judged from Roentgen ray and fluoroscopy, was normal in 37 of 87 (43%) of these patients with aortic insufficiency.

7. In only 3 patients (2.2%) of a total of 135 with syphilitic aortic insufficiency was the blood Wassermann reaction negative in the absence of a history of previous antisyphilitic treatment.

Conclusions. Aortic insufficiency due to syphilis is present in a clinically recognizable form for a relatively lengthy period of time (2 to 10 years) before the development of symptoms.

This asymptomatic form of aortic valvular syphilis is encountered in approximately one-half of the patients with valvular syphilis.

Present-day prognostic data, based as they are on the course following the onset of symptoms of failure, are inapplicable to this large group of patients with cardiovascular syphilis.

There are no available data on the ultimate length of this asymp-

tomatic phase, but it appears from a study of our cases thus far that it can be measured in terms of years rather than months.

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PROLONGATION OF THE P–R INTERVAL IN PATIENTS WITH PAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER FOLLOWING MYOCARDIAL INFARCTION.

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Paroxysmal auricular fibrillation and flutter are among the arrhythmias most commonly encountered in patients with coronary thrombosis. They have also been observed following ligation of a coronary artery in animals.[3] The occurrence of an auricular arrhythmia during the course of myocardial infarction cannot be explained on an anatomical basis since the arteries involved and the infarct itself are always in the ventricular myocardium.

A considerable volume of evidence indicates that experimentally produced auricular fibrillation in animals is due at least in part to vagal activity.[5] The activity of the vagus nerve recently has been implicated in the genesis of auricular fibrillation which occurs in patients with thyrotoxicosis[10] and rheumatic heart disease.[1] It was

therefore of interest to study patients in whom auricular fibrillation occurred following myocardial infarction in order to determine the frequency of other changes in cardiac conduction which might be interpreted as due to increased vagal activity.

Material. The records of all patients were examined in whom paroxysmal auricular fibrillation or flutter first appeared soon after myocardial infarction. Only those with electrocardiographic evidence of auricular fibrillation or flutter within 12 days after a definitely diagnosed attack of cardiac infarction were included in this study. A few were eliminated because no records were made during the periods of normal rhythm, so that no comparative studies could be made. There remained 14 cases suitable for analysis.

Results. All patients exhibited changes in T waves and ST segments considered characteristic of infarction of the ventricle. In addition 9 of the 14 patients showed prolongation of the P–R interval on one or more occasions within a few days prior to or following the onset of auricular fibrillation. In one instance the P–R interval had been prolonged for several years previously. In all 9 instances the P–R interval varied considerably from day to day; in 8 of the 9 cases it decreased to within normal limits at one time or another. The occurrence of prolongation of the P–R interval and the onset and offset of auricular fibrillation were not related to medication or changes in physical signs such as cyanosis, collapse, or congestive failure.

Discussion. Less than 10% of 375 patients with acute coronary occlusion studied by Master *et al.*[8] exhibited a P–R interval greater than .20 second. The fact that 9 of 14 cases or 64% of our patients with paroxysmal auricular fibrillation or flutter after coronary occlusion showed prolongation of the P–R interval, usually transitory, must therefore be considered significant. In the 5 patients who did not show prolonged P–R interval an average of less than four tracings were made during periods of normal rhythm as compared with an average of more than 8 in the other cases; the abnormally prolonged P–R interval may perhaps be found more frequently if electrocardiograms are taken more often. Master *et al.*[8] observed paroxysmal auricular fibrillation in 2 patients with prolonged P–R intervals after coronary occlusion.

In 1937 Bruenn[2] and Keith[6] showed that the prolonged P–R interval seen in acute rheumatic fever is due to increased vagal activity. It has been pointed out in another place[1] that such evidence of increased vagal activity is frequently found in patients with rheumatic heart disease in whom auricular fibrillation develops. Of interest likewise is the fact that repeated injections of acetyl-β-methyl choline in normal unanesthetized dogs gives rise either to auricular fibrillation or to partial heart block, the arrhythmia which will develop being entirely unpredictable.[5] The sequence of events as revealed by electrocardiographic study in patients with auricular

fibrillation following coronary occlusion resembles that seen in dogs receiving repeated injections of acetyl-β-methyl choline.

The cause of the prolonged P–R interval seen in coronary artery disease has not yet been completely elucidated, although available evidence strongly suggests its functional origin. Master and his co-workers[8] found no anatomical lesion to explain it; this is readily understandable since infarction of that portion of the myocardium containing the A–V node is infrequently found at postmortem examination. Moreover, these authors[8] found that atropine shortened the P–R interval in 2 of 3 patients with prolongation of the P–R interval associated with cardiac infarction. Additional work in this regard is however necessary before the vagal origin of prolonged P–R intervals after myocardial infarction can be accepted as proved. Master *et al.*[8] suggested that anoxemia might be a factor in causing a prolonged P–R interval after cardiac infarction. These authors, however, noted its frequent occurrence after the disappearance of evidences of anoxemia. In the present study anoxemia or shock could not be implicated as the factor responsible for the increase in P–R interval. Although prolongation of the P–R interval has been induced by anoxemia in animals[7,9,11] and in man[4] the degree of anoxemia necessary to produce this change is far greater than that observed in cases of heart disease.

The available data, though scanty, suggest that the prolonged P–R interval associated with cardiac infarction is probably the result of increased vagal activity. The occurrence of auricular fibrillation and flutter following infarction of the ventricle therefore becomes understandable since the rôle of vagal acticity in production of auricular fibrillation and flutter in animals[5] and in man in thyrotoxicosis,[10] and rheumatic fever[1] has been pointed out. The origin of vagal impulses which may act on the heart and so give rise to auricular fibrillation following myocardial infarction will be the subject of another study.

Summary. 1. The frequent occurrence of auricular fibrillation and flutter following cardiac infarction cannot be explained as directly due to anatomical findings, since the latter lesions are almost always ventricular.

2. Sixty-four per cent of patients with paroxysmal auricular fibrillation and flutter due to cardiac infarction also have a variable but abnormally prolonged P–R interval within a few days of the onset of fibrillation.

3. Available evidence, though scanty, suggests that the prolonged P–R interval of cardiac infarction is probably due to increased vagal activity.

4. Since increased vagal activity appears to be one factor responsible for the occurrence of auricular fibrillation in general, the occurrence of this arrhythmia following ventricular infarction becomes understandable.

TABLE 1.—*P–R* INTERVAL AND OCCURRENCE OF AURICULAR FLUTTER AND FIBRILLATION AFTER CARDIAC INFARCTION.*

Days after infarction.	*P–R* interval.	Cardiac rate.
	Case 1.	
0	A.F.†	170
1	.20	65
4	.16	60
24	.24	65
30	.22	65
30	A.F.	140
31	.18	65
33	.22	70
42	.18	60
	Case 2.	
0	.14	120
3	.22	120
4	A.F.	140
	Case 3.	
6	.20	120
7	A.F.	160
12	.24	90
	Case 4	
Before	.16	80
1	.22	100
2	.20	90
5	.18	90
Second infarction		
0	A.F.	170
5	A.F.	110
15	.1	90
36	.20	90
	Case 5.	
1	.14	120
2	A.F.	180
7	.16	90
22	.24	90
30	.16	70
	Case 6.	
5	.22	65
7	.20	70
Second infarction		
1	A.Fl.‡	150
2	.20	90
3	A.Fl.	160
6	.22	80
20	.20	80
	Case 7	
Before	.16	70
3	.24	70
4	.18	70
5	A.F.	75
	Case 8.	
1	A.F.	160
2	A.Fl.	140
4	.20	90
14	.22	80
16	.20	80
36	.24	70
	Case 9.	
Before	.26	65
2	.28	85
Second infarction		
2	.16	120
2	A.F.	120
7	.28	55
11	.30	75
	Case 10.	
4	.14	75
11	.16	110
12	A.Fl.	150
14	.16	90
	Case 11.	
3	.16	100
5	A.F	170
20	.16	60
	Case 12.	
3	.16	85
5	A.F.	110
8	.18	70
	Case 13.	
2	A.F.	140
4	.18	75
10	A.Fl.	160
	Case 14.	
1	.16	90
6	A.F.	190
9	.14	80

* A number of repetitive observations have been omitted for lack of space.
† Auricular fibrillation. ‡ Auricular flutter.

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A JUSTIFICATION FOR THE INCREASING USE OF ELECTROCARDIOGRAPHY IN HOSPITAL PRACTICE.

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During recent years there has been a steadily increasing demand for electrocardiography in the clinical study of patients in the New Haven Hospital and Dispensary. That the growing employment of this laboratory aid is only partly attributable to the increasing number of patients is shown by Table 1, which reveals that the ratio of electrocardiograms to the number of patients studied annually has been rising. Since approximately 75% of all electrocardiograms obtained have been on patients in the medical division of both hospital and dispensary, the figures for these may be more relevant and are included also in Table 1. It is evident that during the last 12 years the number of tracings taken on every 100 patients has more than doubled. In the same interval, mortality from heart disease in New Haven has risen slightly less than 20%. It is clear, therefore, that there has actually been a growing general use of electrocardiography in the elucidation of clinical problems.

Table 1.—Annual Ratio of Electrocardiograms per 100 Patients.

Year	1929.	1930.	1931.	1932.	1933.	1934.	1935.	1936.	1937.	1938.	1939.	1940.
Electrocardiograms	319	340	375	548	465	585	627	873	882	1,017	1,369	1,693
All hospital patients	6,551	6,601	7,454	7,343	7,554	8,156	8,871	9,177	9,304	9,628	10,125	12,236
All dispensary patients	8,720	9,780	10,950	13,900	19 068	18,627	16,612	15,440	14,285	15,807	16,136	16,495
Total all patients	15,271	16,381	18,404	21,243	26,622	26,783	25,483	24,617	23,589	25,435	26,261	28,731
Ratio of ECG's per 100 patients	*2.08*	*2.08*	*2.04*	*2.58*	*1.75*	*2.18*	*2.47*	*3.55*	*3.75*	*4.00*	*5.21*	*5.83*
Medical hospital patients	1,170	1,289	1,443	1,391	1,361	1,483	1,499	1,646	1,804	1,912	2,237	2,651
Medical dispensary patients	850	1,050	1,390	1,680	1,869	2,311	1,781	1,558	1,550	1,540	1,594	1,696
Total medical patients	2,020	2,339	2,833	3,071	3,230	3,794	3,280	3,204	3,354	3,452	3,831	4,347
Ratio of ECG's per 100 patients	*15.5*	*14.5*	*13.3*	*17.8*	*14.4*	*15.4*	*19.1*	*27.3*	*26.3*	*29.5*	*35.7*	*38.9*

In the face of such a steadily increasing demand for a laboratory service in relation to the number of patients studied, it is pertinent to inquire whether the augmented laboratory output is being accomplished at a relative loss in clinical value for each 100 electrocardiograms made, to determine whether any data of importance are contributed by the added effort, and to consider whether such additional information justifies the increased cost and the heavier tax on the laboratory facilities and personnel.

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These considerations engaged our attention, and answers to the questions raised were sought by acquiring information under the following three headings:

1. The relation between increasing employment of electrocardiography and the proportion of normal and abnormal records obtained.

2. Estimation of the clinical value of a representative group of electrocardiograms during a year of small demand as compared with a year of large demand.

3. Investigation of the results of *routine* electrocardiograms taken on a large group of patients who would not otherwise have had the benefit of electrocardiographic study.

SECTION I. *Relation Between Increasing Use of Electrocardiography and Proportion of Normal and Abnormal Records Obtained.* All the electrocardiograms obtained during a 12-year period, totalling 9093 records, were divided into three groups as follows:

1. Normal group—including sinus arrhythmia, infrequent ectopic beats, and moderate bradycardia and tachycardia (heart rates between 50 and 120).

2. Abnormal group—all others, excluding those which showed only left axis deviation.

3. Group having left axis deviation, of all degrees, as the only abnormality.

Table 2 and Chart 1 show the total annual output of electrocardiograms from this laboratory for the last 12 years and the number of records that were normal, abnormal, and characterized by left axis deviation only. It is apparent that as electrocardiograms were obtained more and more generally, the proportion of abnormal tracing not only rose steadily but practically paralleled the increase in the total number of records for each year, while the figures representing normal records showed a much more gradual ascent.

TABLE 2.—RELATION BETWEEN INCREASING DEMAND FOR ELECTROCARDIOGRAMS AND PERCENTAGE OF NORMAL AND ABNORMAL RECORDS OBTAINED.

Year.	ECG's taken.	Normal (%).	Abnormal (%).	L.A.D. only (%).
1929	319	32.0	58.8	9.2
1930	340	24.7	65.6	9.7
1931	375	27.8	58.8	13.6
1932	548	33.4	58.0	8.6
1933	465	30.4	53.4	16.2
1934	585	29.6	59.8	10.6
1935	627	34.9	50.4	14.7
1936*	873	25.2	62.8	12.0
1937*	882	21.0	67.0	12.0
1938†	1017	21.5	68.6	9.9
1939‡	1369	24.2	65.2	10.6
1940‡	1693	20.3	69.5	10.2

* Precordial leads taken on about one-third of the patients in this year.

† Precordial leads taken on about two-thirds of patients in this year.

‡ Precordial leads taken routinely on all patients in this year.

Expressed numerically, 58.9% of the electrocardiograms were abnormal in the first 5 years of the 12-year period, while 66.6% were abnormal in the last 5 years. This considerable and unexpected divergence of the curves for the normal and abnormal groups in Chart 1 implies that the rapidly increasing utilization of electrocardiography has not been wasted upon patients without heart disease, and it suggests that perhaps an even greater use of electrocardiography might serve as an important case-finding method.

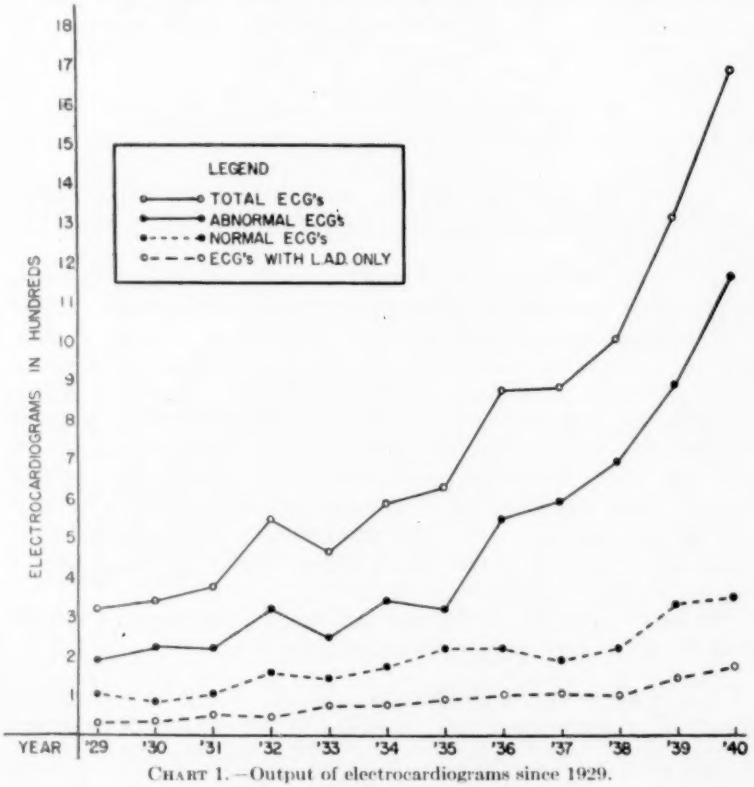

CHART 1.—Output of electrocardiograms since 1929.

Whether the augmented laboratory service actually contributed anything of real significance to the clinical study of patients seemed to be the next logical inquiry, for the proportion of normal to abnormal records is not strictly indicative of the clinical usefulness of the tracings.

SECTION II. *Estimation of the Clinical Value of Representative Groups of Electrocardiograms During a Year of Small Demand as Compared With a Year of Large Demand.* One hundred electrocardiograms were drawn from the laboratory files of 1934, a year of relatively low demand, and another hundred were taken from the

files of 1939, a year in which the demand was about twice as great as in 1934. The records selected were evenly distributed throughout each year, the quotient of the year's output divided by 100 being the interval between the serial numbers drawn: in this way we tried to avoid error arising from professional idiosyncrasies which might have prevailed in the ordering of the electrocardiograms at any period. Excluded from this study were tracings of patients who were already represented in this particular investigation by an electrocardiogram previously drawn.

Each electrocardiogram was then appraised as to its clinical value from a study of the case history. Each tracing was then classified as follows:

Class I: Records of decisive and exceptional significance in that they contributed distinctly new information to the clinical knowledge of a case.

Class II: Records with positive significance, either in confirming a clinical impression or definitely establishing a diagnosis which had been uncertain.

Class III: Records without positive significance whether normal or abnormal, and considered lacking in clinical helpfulness.

The classes were subdivided into two groups: Group A were normal electrocardiograms, and Group B were abnormal records. We sought also to determine whether in the year of greater call for electrocardiography there was evidence of less discriminating use of this laboratory aid. This was attempted by passing judgment on each record in Class III as to whether or not it appeared justified from a careful consideration of the clinical features. This was admittedly a somewhat arbitrary procedure, yet the independent deliberations of each of the three authors resulted in unanimity of opinion in all but a very few cases.

The basis of classification of the electrocardiograms may be clearer from the following examples of actual cases:

Class I, *Group A*. A middle-aged man was ill with typical clinical features of coronary thrombosis. Serial ECG's, of which the one considered here was the first, were all normal, and rendered this diagnosis untenable. This led to a suspicion of dissecting aneurysm which was finally diagnosed.

Group B. An elderly man under study for sudden severe headache and gastro-intestinal disturbance followed by dyspnea had a "routine" ECG which unexpectedly showed signs of acute myocardial infarction (with typical evolution of T-wave abnormalities in subsequent serial records).

Class II, *Group A*. An old woman with a history vaguely suggesting coronary thrombosis had a normal ECG, which was regarded as helpful in excluding the improbable diagnosis.

Group B. One 35-year-old man with a history suggesting coronary thrombosis had an ECG showing abnormalities compatible with but not typical of myocardial infarction. Another older patient with a similar history had classical ECG changes for anterior apical myocardial infarction. Both records supported the clinical impression and were therefore regarded as helpful.

CLASS III, *Group A* (justified). A middle-aged man with hypertension was suspected of having heart disease on this basis but definite evidence was lacking. ECG also was normal, therefore not positively helpful, yet thought to be justified.

Group A (unjustified). A young man with gigantism and psychoneurosis with respiratory symptoms, palpitation, and precordial discomfort had no abnormal cardiovascular findings and an ECG was normal. A second ECG, drawn in this study, was the same as the first, therefore considered unhelpful, and deemed unjustified since there were no new indications for its being repeated.

Group B (justified). A middle-aged woman with hypertension had been under treatment with digitalis for heart failure for several years. The ECG drawn in this study showed I–V block. Because similar findings had been disclosed 2 years before, this record was regarded as unhelpful yet justified at least because of the long interval between the examinations.

Group B (unjustified). An elderly man with known arteriosclerotic heart disease with auricular fibrillation. A first ECG showed the abnormal mechanism as well as left axis deviation and S–T and T changes of the variety due to digitalis. Another ECG, drawn in this study, was requested only a few days later without new indications, and the tracing was similar to the first. The second record was therefore deemed unhelpful and unjustified.

TABLE 3.—EVALUATION OF ELECTROCARDIOGRAMS IN A YEAR OF SMALL DEMAND AND A YEAR OF LARGE DEMAND.

	1934. 100 ECG's.	1939. 100 ECG's.
Class I (diagnostic*):		
Group A—Unexpectedly normal	0	2
Group B—Unexpectedly abnormal	16	12
Total	16	14
Class II (helpful):		
Group A—Normal	5	7
Group B—Abnormal	34	40
Total	39	47
Class III (unhelpful):		
Group A—Normal	14	20
Group B—Abnormal	31	19
Total	45	39

* Diagnostic in sense that unexpectedly new clinical data of importance resulted.

It is acknowledged that the two samples of 100 records are too small to permit statistical treatment, but the analysis as summarized in Tables 3 and 4 reveals interesting trends.

It is notable that in 1939, when electrocardiography was used about twice as frequently as in 1934, the percentage of insignificant or unhelpful records (Class III) was smaller, while the percentage of clinically helpful records (Classes I and II) was definitely larger (Table 3). Moreover, there were only about half as many seemingly unjustified records in the year of greater demand (Table 4). If one grants the liberal view that all of the Class I and II records were justified, then 85% of the tracings in 1934 and 92% in 1939 fall in this category. The actual differences in support of these observations are small, but the trend in the direction indicated, rather than

the opposite one, seems to us convincing evidence that the greater volume of work in the latter year was profitably expended.

That the greater clinical value of the records in 1939 was not due in any important respect to the routine employment of a precordial lead in this year was excluded by a specific inquiry which revealed that among the 100 electrocardiograms, of which 71 were abnormal, there were only 3 in which the interpretation of abnormality was dependent primarily or entirely on changes occurring in Lead IV-F.

TABLE 4.—JUSTIFICATION OF CLASS III (UNHELPFUL) ELECTROCARDIOGRAMS DURING A YEAR OF SMALL DEMAND AND A YEAR OF LARGE DEMAND.

Year.	Group.	Justified.	Unjustified.
1934 (45 ECG's)	A (normal)	10	4
	B (abnormal)	20	11
	Total	30	15
1939 (39 ECG's)	A (normal)	17	3
	B (abnormal)	14	5
	Total	31	8

SECTION III. *Inquiry Into the Value of Routine Electrocardiography.* We proceeded to investigate whether a significant amount of cardiac abnormality was being overlooked through the practice of obtaining electrocardiograms only when they seemed clinically indicated to the staff. We therefore undertook the following experiment.

Electrocardiographic observations were made on 300 patients from all divisions of the New Haven Hospital and 100 patients from the medical clinic of the New Haven Dispensary. All were patients for whom electrocardiograms were *not* requested in the ordinary course of the clinical study. Selection was exercised only in that subjects less than 13 years old were not included. In the interests of economy of materials and time most of these examinations were made with an amplifier type electrocardiograph whose galvanometer deflections were observed directly on a slowly-moving fluoroscopic lag-screen belt illuminated with horizontal millimeter lines and vertical 0.1 second time subdivisions.* The accuracy of these observations was verified by obtaining a conventional electrocardiographic record whenever there was doubt as to whether the measurement or character of any feature was within normal limits, and the interpretations of such permanent records were then compared with our notes based on the direct visual method; only a very few minor discrepancies were encountered. Electrocardiograms of the three usual limb leads and precordial Lead IV–F were studied.

In order to avoid influencing the professional house and attending staffs in their ordering of electrocardiograms on patients in the hospital, the investigation was done surreptitiously, usually over

* Sanborn cardiette and cardioscope.

week-ends, and information acquired by us was not divulged until the study was completed. We discarded and made substitutions for cases in which electrocardiograms were subsequently formally requested during the patient's hospitalization. In performing the 100 examinations in the out-patient clinic, only new patients were taken, they were chosen at random, and the observations were made early in the morning while the patients were awaiting the opening of the clinic. The case history pertaining to each of the 400 electrocardiograms was later searched for data and opinions bearing on the presence or absence of cardiovascular disease.

These examinations were conducted sporadically over a period of 9 months, chiefly in May and November, so that seasonal factors concerned in the type of cases admitted were partly controlled. During this time there were several changes in professional staff, and personal factors which might influence the frequency of calling for electrocardiographic aid were thus minimized.

TABLE 5.—ABNORMALITIES ENCOUNTERED AMONG 400 UNREQUESTED ROUTINE ELECTROCARDIOGRAMS.

Age group	13–29.	30–39.	40–49.	50–59.	60–69.	70+.	Total.	13–35.	36–49.	50+.
Number of ECG's	113	67	73	67	54	26	400	151	102	147
Normal ECG's	93	41	36	16	20	7	213	120	50	43
Moderate L.A.D.	3	15	19	23	12	6	78	11	26	41
Abnormal ECG's	17	11	18	28	22	13	109	20	26	63
	15.0%	16.4%	24.7%	41.8%	40.3%	50%	27.2%	13.2%	25.5%	42.9%
A–V block	1		1	1			3	1	1	1
I–V block			3	2	4	2	11		3	8
L.A.D. (marked)				1	2		3			3
R.A.D.	1			2			3	1		2
Abnormal QRS$_4$	1	1	2	1	2		7	1	3	3
Low voltage	5	5	3	5	4		22	6	7	9
Abnormal S–T	1			1			2	1		1
T_1 abnormally low		1					1		1	
T_1 flat, inverted				2		1	3			3
T_2 inverted, diphasic				1		1	2			2
T_3 deeply inverted	1						1	1		
T_4 inverted, diphasic	3	2	2	1	2	1	11	5	2	4
T abnormal in 2 leads or more	4	2	7	11	8	8	40	4	9	27

Each ECG is represented by the single most important abnormality it presented.

ECG abnormalities were established by the following: P–R interval in excess of 0.20 second. QRS duration in excess of 0.10 second. QRS amplitude not exceeding 0.5 mv. over all in the limb leads. Q wave in Lead IV–F more than 0.3 mv. in amplitude. R wave absent in Lead IV–F. Left axis deviation only when marked. Right axis deviation. S–T displacement of more than 0.1 mv. T-wave amplitude of less than 0.1 mv. in Leads I or II. T-wave inversion or diphasia in Leads I, II, and IV–F. T-wave inversion of unusual depth (5 mv.) in Lead III (one instance).

Not included among ECG abnormalities were the following: P-wave deformities. Very slight slurring of QRS. Low voltage of QRS in Lead IV–F only. Prominent Q wave in Lead III. Isoelectric T wave in Lead IV–F.

The results of this inquiry are summarized in Tables 5 and 6, from which it is seen that while 109 (27.2%) of the electrocardiograms were abnormal, some abnormality might have been expected in 60 (15%), but was an entirely unexpected finding in 49 (12.2%) of the patients examined. No patient was included in the "unexpectedly abnormal" group whose blood pressure exceeded 150 systolic or 95 diastolic. Moreover, if any detail in the recent history or physical findings had a possible cardiac implication the record was excluded from this group. Even after eliminating 22 cases

showing only low voltage (a net QRS amplitude not exceeding 5 mm. in the limb leads), and an instance of right axis deviation in a young woman, since these may not always establish organic disease of the heart, there were still 86 (21.5%) of the 400 examinations that revealed changes which are usually considered definitely abnormal, and of these 31 (7.8%) were unexpected. Furthermore, it is worth emphasizing that while the number of abnormal electrocardiograms in this group cannot easily be made smaller (see Discussion), there are several possibilities that it might actually be larger. Thus, although no borderline records are included in the group and even tracings with left axis deviation of moderate degree were excluded, some of these may well imply cardiac abnormalities in certain of our patients. Also, we ignored Q–T measurements entirely, yet there is evidence that prolongation of this interval beyond certain definite limits may indicate cardiac abnormality.[1] Moreover, in these *single* electrocardiographic examinations we may have overlooked the pathologic significance of records whose features were within normal or borderline limits, yet which possessed changes indicative of cardiovascular abnormality that would have been evident from serial studies. The importance of serial changes, even when slight, is well known[7] and has been abundantly confirmed in our experience.[4] Finally, a few cases were excluded from the "unexpectedly abnormal" group on the basis of a single blood pressure determination in which either a systolic or a diastolic reading exceeded our established limits but did not necessarily prove the existence of true hypertension or hypertensive heart disease. Even when the electrocardiographic abnormalities bore no conceivable relation to the abnormal clinical features, as in the case of a young woman with a craniopharyngioma and paroxysmal hypertension and with deviation of the electrical axis to the right, our convenient but conservative rule obliged inclusion of the case in the "expectedly abnormal" group.

TABLE 6.—EXPECTANCY AND FINDINGS OF NORMAL AND ABNORMAL ELECTROCARDIOGRAMS AMONG 400 UNREQUESTED ROUTINE RECORDS.*

Age group:	13–29.	30–39.	40–49.	50–59.	60–69.	70+.	Total.	13–35.	36–49.	50+.
Expected normals	*100*	*61*	*51*	*33*	*22*	*10*	*277*	*135*	*77*	*65*
Actual normals	87	37	28	13	15	4	184	111	41	32
Abnormals	11	10	13	9	3	3	49	14	21	15
Borderline	2	14	10	11	4	3	44	10	16	18
Expected abnormals	*13*	*6*	*22*	*34*	*32*	*16*	*123*	*16*	*25*	*82*
Actual abnormals	6	1	5	19	19	10	60	6	6	48
Borderline	1	1	9	12	8	3	34	1	10	23
Normals	6	4	8	3	5	3	29	9	9	11

* Expectancy based on clinical findings and impressions.

Another fact of particular interest which emerged from this study was that electrocardiographic abnormalities occurred in 15% of the

subjects less than 30 years of age whose histories, physical signs, and clinical impressions gave no suggestion of cardiovascular disease. The relatively high incidence of abnormalities in the tracings among the elderly patients, even in the absence of other clinical evidence of heart disease, was perhaps to have been expected and has recently been emphasized by others also.[5,6] In the younger age groups, however, these findings came as a surprise.

Because of the possible bearing of these observations on the judgment of physical fitness of men called to arms under the Selective Service Act, the age groups were recast to show the results among subjects through the draft age, as compared with middle-aged and elderly groups. Definitely abnormal electrocardiograms occurred in 13.2% of the youngest group without other clinical evidence of heart disease; if the borderline feature of left axis deviation is included, 20.5% of the group within the draft age were not normal. Since these observations are confined to a population made up of patients they are not necessarily applicable to the general population.

It is pertinent to the subject of routine electrocardiography to refer briefly to unpublished observations, carried out previously in this laboratory by A. D. Chidsey,[2] on electrocardiographic abnormalities encountered in the examination of patients with acute infectious diseases. Fifty subjects suffering chiefly from pneumonia, scarlet fever, and acute tonsillitis and pharyngitis, were selected for study because they had no history or physical signs of cardiac or vascular disease, were free from hypertension, and had received no drugs like digitalis or quinidine. Electrocardiograms, including the three limb leads and precordial Lead IV–F, were taken at 4- or 5-day intervals both at the height of the illnesses and during convalescence. In 22 of the patients (44% of the group) electrocardiograms that were judged either probably or definitely abnormal were obtained. Fifteen of the patients (30% of the group) exhibited definite abnormalities, either RS–T and T changes or delayed A–V conduction, which in all but one instance were transient or changing during the serial studies. A descriptive tabulation of this group of cases is presented in Table 7 (Chidsey's Table 4). Since the average age of these 15 patients was 25.6 years, of whom the 2 oldest were 42 and 43 years of age, respectively, not even asymptomatic coronary sclerosis can be invoked in explanation for the observed abnormalities, and it is believed that the serial changes indicated an acute myocardial involvement that was not evident clinically.

Electrocardiography seemingly offers an important case-finding method in the field of cardiovascular disease even among the relatively young who have had the benefit of examination and study by two or more physicians under hospital conditions. It appears that the routine employment of this laboratory aid discloses a significant incidence of electrocardiographic abnormality beyond that which might be expected from other clinical evidences.

TABLE 7.—FIFTEEN CASES SHOWING DEFINITE ELECTROCARDIOGRAPHIC ANOMALIES.

Case No.	Sex, Age.	Diagnosis.	No. of ECG's.	EKG changes.
6	M 23	Virus (?) pneumonia	3	T wave low and flat in all leads reverted to normal.
23	M 42	Lobar pneumonia	4	T wave low and flat in Leads I and II and diphasic in IV–F reverted to normal; prolonged Q–T throughout.
24	M 18	Lobar pneumonia	5	T wave low and flat in all leads reverted to normal.
27	F 7	Scarlet fever	6	T wave in Lead IV–F changed from upright to inverted and returned to upright; P–R interval changed from normal to prolonged and returned to normal; prolonged Q–T throughout.
30	M 27	Lobar pneumonia	3	T wave low and flat in Leads I and II reverted to normal in Lead I.
31	F 43	Acute pharyngitis	3	T wave low and flat in Lead I returned to normal; T wave in Lead IV–F changed from upright to inversion to diphasic.
32	F 10	Scarlet fever	4	T wave low and flat in Lead II returned to normal; T wave in Lead IV–F changed from upright to inversion, to upright; prolonged Q–T throughout.
37	F 14	Peritonsillar abscess	3	T wave in Lead IV–F changed from low to inverted with a high *S–T* level and then to diphasic.
40	M 29	Scarlet fever	5	T wave in Lead I changed from normal to inverted with low S–T segment level and returned to normal; in Lead II changed from normal to low and flat, and returned to normal; in Lead IV–F changed from diphasic to inverted and returned to normal; prolonged Q–T in second record.
41	M 40	Peritonsillar abscess	3	Incomplete A–V block throughout; P–R interval 0.22 second.
42	F 24	Pneumonitis	2	T waves flat in Leads I and II with low S–T segment in Lead IV–F returned to normal.
45	M 19	Lobar pneumonia	5	T wave in Lead I flat and low returned to normal; T wave in Lead IV–F deeply inverted returned to upright; abnormal QRS in Lead IV–F throughout; prolonged Q–T throughout.
47	M 30	Lobar pneumonia	3	Incomplete A–V block throughout; P–R interval 0.22 to 0.26 second; T wave in Lead II low returned to normal, and in Lead IV–F diphasic returned to normal.
48	F 40	Erysipelas	4	Abnormally large and notched P waves in Leads II and III returned to normal.
49	M 18	Meningococcemia	3	T wave in Lead II low and flat with deeply inverted T wave in Lead III returned to normal in Lead II; prolonged Q–T in second record.

Discussion. It is illogical to presume that the steady increase in the proportion of abnormal electrocardiograms as more and more tracings were made annually (Section I) was primarily attributable to the more frequent resort to this diagnostic method; for although heart disease may now be called "captain of the men of death," it is certainly not yet an associate of the majority of the sick, and the relative occurrence of electrocardiographic abnormalities would show a decreasing increment as abnormal records are looked for more generally and with less discrimination. We believe, therefore, that these observations, together with the unexpected results of the samplings dealt with in Section II imply a more judicious and intelligent application of this laboratory aid coincidental with its increased employment, and from this one may, further, infer that a more liberal use of this diagnostic method does not necessarily result in wasteful expenditure of laboratory service. The additional discovery of a considerable number of electrocardiographic abnormalities in a significant proportion of patients who were regarded as free from cardiovascular disease (Section III) is direct evidence in support of a prevalent view that a full appraisal of the cardiac status is not complete without this adjunct to supplement the history, physical examination, functional tests, and roentgenographic study.

As to the significance of the unexpected abnormalities encountered, a valid general appraisal is admittedly difficult to make.

In the first place, the bases upon which we separated the expected from the unexpected abnormalities were necessarily arbitrary even though our approach was deliberately objective. Nevertheless, modification of the criteria of judgment in one direction or another does not enhance the results. Thus, if the clinical features that define an unexpected abnormality are made narrower and more rigid, the number of unexpectedly abnormal records naturally rises; while, if the clinical features defining an unexpected abnormality are made broader and more inclusive, the number of normal tracings increases unreasonably.

In the second place, some of our unexpectedly abnormal records might be explained, *a posteriori*, by a history like that of trichinosis some years before or diphtheria in childhood. If the validity of such explanations could be established, then some of the unexpected abnormalities we encountered may have no present or future clinical importance at all. However, in other patients the discovery of similar unexpected abnormalities may be highly significant. For example, T-wave abnormalities or heart block (A–V or I–V) in the diabetic patient or the subject with Buerger's disease may imply current coronary heart disease and progressive cardiac damage with definite prognostic inferences.

Thirdly, although a considerable portion of the electrocardiographic abnormalities was found among the older age groups, this might not be considered surprising, for coronary heart disease is common among them, the nature of such heart disease is particu-

larly prone to produce electrocardiographic alterations, and changes in the tracings are more to be expected in any heart disease as it ages with advancing years. As a matter of fact, the occurrence of unexpected abnormalities was consistently lower in the older than in the younger age groups with the criteria we followed. Old age *per se* is not a cause of such abnormalities. It seems quite likely, therefore, that the unexpectedly abnormal electrocardiograms in the older patients indicate cardiac involvement not otherwise apparent.

Finally, the actual significance of certain familiar electrocardiographic abnormalities is not yet clearly established, for the category of abnormal features is built up largely from studies on patients with known or suspected heart disease instead of statistical analyses of large groups of normals. For example, low voltage occurred in 22 of the 400 patients examined in Section III of this study, and in 18 subjects this finding occurred in the absence of any presumptive evidence of heart disease. Wilson[10] found low voltage in less than 1% of 100 normal subjects, which suggests that this feature was abnormal. However, Willius and Killins[9] stated that in 68% of 140 cases showing low voltage there was no apparent heart disease, and unpublished studies[3] made in this laboratory of 50 cases exhibiting low voltage included 15 patients in whom heart disease was not otherwise established. Thus, while low voltage may be an electrocardiographic abnormality, its significance and relation to heart disease is still uncertain in our opinion. Similar considerations may perhaps apply to other electrocardiographic abnormalities, such as unusually low, flat, or diphasic T waves.[8] The serial changes in T noted by Chidsey[2] in patients with acute infectious diseases suggest at least transient myocardial involvement. Perhaps such changes mean no more than abnormal findings in the urine encountered transiently in conditions other than primary disease of the kidneys, but the facts indicate that the electrocardiogram, like the urine analysis, may furnish evidence of such involvement which may not otherwise be clinically apparent, and may influence views bearing on diagnosis, prognosis, and convalescence, the validity of which can be proved only by further experience.

If on the other hand, most of these abnormalities should prove meaningless, then our unexplained abnormal findings are but few and may cause no further concern. We are not prepared, therefore, to recommend electrocardiography as a routine examination, although it appears fully as capable of revealing obscure disorder as the more conventional routine blood count and urine analysis. Our results oblige us, however, to view electrocardiography as a desirable laboratory test not only in cardiac patients but also in those with diseases that are known or suspected to involve the heart secondarily, and in all elderly subjects. Our study indicates that wide general use of this laboratory method is amply justified by its

frequent disclosure of unexpected abnormalities which may prove to imply cardiac involvement that would otherwise escape detection.

Summary. Inquiry into the clinical helpfulness of a large and steadily increasing demand for electrocardiograms in the New Haven Hospital and Dispensary revealed that the proportion of abnormal records obtained has grown considerably and has practically paralleled the increasing demand, and that the clinical value of a representative group of records in a year of high demand was fully as great as in an earlier year when records were requested only half as frequently.

A study of the results of routine electrocardiography disclosed a significant incidence of electrocardiographic abnormalities beyond that which might be expected from other clinical evidence.

Conclusion. The increasing use of electrocardiography in local hospital practice appears justified. Requests for routine unnecessary electrocardiograms are decried, but their liberal use, if applied judiciously and intelligently, discloses abnormalities of clinical value sufficient to warrant the extra expenditure of laboratory service.

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THE DANGER OF PROCRASTINATION IN BILIARY TRACT DISEASE UNTIL IRREVERSIBLE LIVER AND KIDNEY CHANGES OCCUR.

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The terminal phase of biliary tract and liver disease is the result of the progression of certain events, the pattern of which appears to be uniform. The pattern has been labeled "cholemia" misleadingly, for the picture is not entirely dependent upon the presence of icterus or hyperbilinuria. A much better term would be "hepatic insufficiency." Most of the cases presented, in addition, evidences of severe renal (hepatorenal syndrome) damage. While the picture is outwardly more or less uniform, many inconstant, interesting and unexpected functional and pathologic phenomena have occurred in other organs, showing that the results of hepatic insufficiency are far-flung.[6a–e]

The exact factor in hepatic insufficiency which is responsible for the various organ changes is at the present writing unknown. The observation that necrosis of liver cells was associated with changes in the renal parenchyma and consequent renal insufficiency led some men to postulate the liberation of a nephrotoxic poison from the necrosed liver cells. Helwig and Schultz[4] in cases of liver pulpification, and Fitz-Hugh[2] in cases of common duct obstruction with infection believed the mechanism to be definitely nephrotoxic, and incriminated infection as the chief cause. The association of liver damage and renal insufficiency has been reported too often to be merely a coincidental finding. However, there is little experimental proof for this relationship. The association may be merely the result of a disturbed water balance and Mann's[5] work on hepatectomized animals would tend to corroborate this. Edema occurs in hepatic insufficiency, but this may be the result of cardiac failure or of a disturbed relationship of blood proteins which occurs in liver disturbances. It is even conceivable that the hepatorenal syndrome may be the result of an absence or diminution of some factor, possibly hormonal, which is elaborated by the liver. Bile retention does not cause the profound changes, since jaundice is not necessarily a part of the picture. Though biliary nephrosis is not uncommon in obstructive jaundice, these patients may go for long periods of time without developing hepatonephritic toxemia. Circulatory vasoconstriction or vasodilatation has been adduced as a possible cause of these interrelated hepatorenal changes because of their intimate embryologic blood supply.

The clinical picture of biliary tract and hepatic disease terminating with oliguria, anuria and uremia is fairly well known. I have observed this quite frequently and feel that this is a common mode of exitus, but I do not believe that the effects are specific for the kidneys alone. In 10 cases which came to postmortem examination the hepatorenal syndrome was applicable to 6. In 3 cases the predominant terminal phase was cardiac and 1 case presented an unusual blood picture resembling a subleukemic myelogenous leukemia.

It has been my observation that in common duct obstruction the outcome is favorable, provided infection does not set in in the biliary tree. Once infection gains a foothold, whether the obstruction is relieved or not, the entire picture changes and the course is frequently rapidly downhill. Operative release of common duct obstructions is often too late subsequently to reverse the preceding sequence of events. The resulting cholangiohepatitis does not bear any relationship to any particular bacterial organism, although the latter is probably derived from the alimentary canal. The quantitative extent to which the liver parenchyma is functionally involved will determine the final outcome, but frequently there are no recognizable corresponding anatomic changes. Oertel, Stadelmann and Eppinger, Jr., have pointed out that some activity liberated in the

liver cell environment disturbs the normal cell function so that it is unable to neutralize the toxins which result from normal digestive processes or other sources. Infection in the biliary radicals is not the only means of causing sufficient liver damage to produce the terminal picture, for direct trauma with pulpification of the liver and other mechanisms have produced the liver-kidney syndrome.

In my cases the characteristic changes found in the kidneys were marked degenerative changes in the tubules, and at times in the glomeruli, with occasional hemorrhages in the renal parenchyma. One case presented miliary abscesses. Myocardial changes, when present, were also of a degenerative nature. The case presenting an unusual blood picture showed hyperplasia of the myeloid structures. All cases presented a severe degree of periportal cellular necrosis of the liver.

Case Reports. Case 1.—For the preceding year a 52-year-old woman had complained of abdominal cramps, gastric eructations, epigastric pain radiating to the back and right shoulder, without jaundice or change in the color of the stool. The patient was not acutely ill, but was elderly in appearance and obese. The laboratory findings included: 1, Roentgen ray visualization of a single gall bladder stone; 2, icteric index of 11.2; 3, an indirect Van den Bergh of 0.7 unit; the other findings were of no particular importance.

The operative exploration showed: pericholecystitic adhesions, a chronic cholecystitis with one large stone and an old healed duodenal ulcer. For 3 days the patient seemed to do well, then fever developed; there were questionable signs in the left lung; there was rapid subsequent deterioration and exitus occurred on the following day.

The postmortem examination showed: periportal inflammation in the liver parenchyma with fatty infiltration in a cirrhotic environment and an acute parenchymatous nephritis.

This is the more or less typical case of chronic gall bladder disease with subacute cholangitic infection which terminates fatally within a few days after operation, the trauma of operation probably acting as an impetus for the infection to become more fulminating. Although the laboratory study was inadequate, the clinical course indicated that this case terminated with renal failure, since outside of the liver the chief histologic changes were found in the kidneys.

Case 2.—A 65-year-old patient was admitted in a second abdominal episode with jaundice, daily chills and fever, and right upper quadrant pain of 6 days' duration, after a free interval of 5 years. The pain was not severe but the jaundice had deepened, the stools had become yellow and the urine very dark. A persistent hiccough was present.

The patient was an elderly, well-developed, rather obese, white male, markedly icteric, acutely ill, and in very bad general condition. The abdomen was slightly distended; and there was marked costal tenderness and percussion tenderness over the lower right ribs. The liver was enlarged to 3 cm. below the costal margin. No other masses or viscera were palpable. The rest of the examination was relatively negative.

Although operation appeared urgently indicated, the patient's general condition was too precarious for any form of surgery. There were toxemia, chills and high fever, a clay-colored stool, increasing abdominal distention,

oliguria, a non-protein nitrogen of 117 mg. per 100 cc. and an increase in the icteric index. The patient died.

The important laboratory data were the following: icteric index, 94.5 to 137.3; Van den Bergh, direct immediate and 17 units indirect; blood urea, 31.1 mg.; non-protein nitrogen, 117.6 mg.; creatinine, 2.73 mg.; urine, bile ++++; blood culture, *B. subtilis*.

This case presented the severest type of liver-induced injury to the renal mechanism. The terminal picture included oliguria, anuria and uremia, and the azotemia was well marked quantitatively.

Case 3.—A 60-year-old white female, comatose and in moribund condition, had had during the preceding year progressive anorexia, bronzing of the skin, and loss of weight. An acute episode of severe right upper quadrant pain had ushered in the present emergency. There were marked toxemia, emaciation, dehydration and jaundice. Many of the toxemic manifestations were referable to the central nervous symptoms. The only objective findings were marked tenderness in the right upper quadrant and a slightly enlarged liver. Death occurred on the day following admission.

Laboratory data included: hemoglobin, 102%; red blood count, 5,200,000; white blood count, 23,500; neutrophils, 50%; urine, smoky, acid, no albumin, small number of casts; Wassermann and Kahn, negative. Blood chemical studies: sugar, 178.6; urea nitrogen, 21; non-protein nitrogen, 21; uric acid, 3.6; creatinine, 1.28; icteric index, 63.3; Van den Bergh direct immediate; indirect 5.1 units/100 cc. serum.

This case presented the picture of a long-standing progressive obstructive jaundice in which the hepatic insufficiency intervened suddenly, probably as the result of a sudden complete tightening of the obstruction, no doubt precipitated by an overwhelming infection. The ensuing toxemia was marked by symptoms referable to the central nervous system.

Case 4.—Ten days before admission, a 58-year-old man, the subject of angina pectoris for the preceding 7 years, complained of epigastric pain which was followed by a gradually increasing, intense jaundice. Weakness and languor were marked at the onset and for the 2 days before admission, mental changes were evident: restlessness, delirium, and finally coma.

The physical examination revealed an elderly well-nourished, extremely restless, comatose, cyanotic individual, with stertorous breathing, and marked jaundice. Pupils were slightly irregular, dilated, fixed to light and slow nystagmus was present. There were exophthalmos and markedly icteric scleræ but the fundi were normal. The lungs were emphysematous. The cardiac sounds were distant, and a harsh systolic blowing, non-transmissible murmur was present at the apex. The area of liver dullness was distinctly diminished. No other masses or viscera were palpable. There was marked hyperreflexia, with bilateral ankle clonus and Babinski. The abdominal and cremasteric reflexes were absent. The rest of the physical findings were of no clinical importance.

There was definite oliguria with terminal anuria. The urine contained a large amount of albumin, an occasional red and white blood cell and many hyaline and granular casts. However, no leucine or tyrosine crystals were present; and there was no glycosuria or acidosis. Bile and urobilinogen were present in the proportion of 1:10.

The blood chemical studies were as follows: glucose, 61.7 mg.; non-protein nitrogen, 67.4 mg.; creatinine, 1.21 mg.; chlorides, 410 mg. per

100 cc. whole blood; CO_2 combining power, 30.5 vol. %; icteric index, 61.9; Van den Bergh—immediate direct, 5.3 units indirect. The Wassermann and Kahn tests were negative and no heavy metals or other poisons could be found in the gastric contents. The hemoglobin was 92%; the red cell count was 4,900,000; the white blood cells numbered 21,800 with 83% neutrophils.

The patient lived for 14 hours after admission to the hospital. There were terminal fever, restlessness, flaccidity and Cheyne-Stokes respiration. Death occurred in cardiac collapse.

This case presented the picture of a subacute yellow atrophy with severe renal impairment and with unusual cerebral symptoms. It is possible that the hyperglycemia may have contributed to the picture, but it is apparent that the cerebral symptoms are out of proportion to the degree of demonstrable anatomic change.

Case 5.—A 40-year-old female, who had had 2 children, was admitted because of pain in the right upper quadrant radiating to the back. The last menstrual period 2 weeks before admission was unusual in that she bled for 10 days. Since the onset there were progressively increasing jaundice, clay-colored stools, pruritus, nausea, anorexia, weakness and a loss of 15 pounds in weight; and, although there had been no further attacks of abdominal pain, a sense of soreness persisted in the back.

The physical examination revealed a middle-aged, well-nourished, markedly jaundiced, white female, in whom there was practically no palpatory localizing signs.

On admission the patient complained of nausea and a feeling of weakness. On the seventh and eighth days she had a slight chill and a rise of temperature to 103° F. An unusual blood picture, namely, an aplasia of the blood elements then developed until the white cell count fell to 350 cells with marked relative lymphocytosis. A number of myeloblasts were found on careful search. The red blood cell count, hemoglobin content and the number of the platelets likewise kept falling. Transfusions were without avail. A myeloid leukosis was suspected but a sternal marrow puncture revealed nothing diagnostic. The icteric index, which had previously been rising steadily, began to fall with the onset of the fever. Urobilin appeared in the stools and urine. The cholesterol esters began to fall. Urine excretion was abundant even in the presence of an increasing azotemia. The phenolsulphonephthalein excretion was undeterminable. Toward the end, there were increasing weakness, dyspnea, elevated temperature, muscular twitchings, delirium and terminal coma; exitus finally occurred.

This case was unusual in that the hematologic picture showed a rapidly progressive aplasia of all the blood elements with the appearance of very immature myeloid cells, so that antemortem, the diagnosis of myelogenous leukemia was made. The histopathology did not bear this out, and again we have an illustration that liver damage may have widespread, protean and, at times, most unusual and bizarre effects.

Case 6.—A 45-year-old, obese, white woman was admitted to the hospital because of frequent episodes of nausea, retching without vomiting, and intermittent attacks of severe hypochondriac pain. Finally, pruritus was present; the urine became dark and the stools clay-colored; marked jaundice developed. Nevertheless, the patient was relatively comfortable and did not appear acutely ill. There were several small hemorrhagic spots on the

abdomen. The heart and lungs were negative. There was marked tenderness with some rebound tenderness in the right upper quadrant, but without rigidity. No masses were palpable, but the liver was slightly enlarged.

The laboratory data included the following: Wassermann and Kahn tests, negative; hemoglobin, 110%; red blood count, 5,400,000; white blood count, 6700 with 70% neutrophils. Blood chemical studies: chlorides, 271.1 mg.; glucose, 99.5 mg.; urea nitrogen, 114.8 mg.; uric acid, 219 mg.; icteric index, 191.4; Van den Bergh, indirect, 18 units; bleeding time, 2 minutes; coagulation time, 5½ minutes; urine, yellow, acid, sp. gr. 1.016, 4+ bile, no urobilinogen, occasional leukocyte; stool, no bile salts present.

After preliminary, not completely satisfactory preparation, she was operated upon. A chronically diseased gall bladder was found, and stones were present in the gall bladder and in the common duct. The patient did well for 8 days. Then she became drowsy and the temperature rose to 102° F. A diffuse erythema multiforme-like rash appeared, with oliguria, drowsiness and terminal coma. Exitus occurred on the fourteenth day.

The postmortem examination demonstrated an obstructive jaundice due to stenosis of the common bile duct and stones; a toxic hepatitis; an acute nephritis; multiple abscesses of kidneys; and a localized plastic peritonitis. The liver showed marked destructive changes with attempts at a compensatory hypertrophy; diffuse fibrous rupture of the bile capillaries and hemorrhagic infiltration of parenchyma; dense fibrosis in areas with almost complete obliteration of the normal liver elements. The kidneys showed diffuse hemorrhagic and degenerative changes in the tubules and glomeruli.

This case presented an unrelievable common duct stenotic obstruction with hepatic insufficiency. A fatal termination was inevitable. Although the case is presented as an example of the liver-kidney syndrome, the general infection and the local suppurative foci in the kidneys and in the peritoneum must not be lightly dismissed, and were surely the final irreversible and dominant cause of death. This association occurs so often that its importance must be stressed.

Case 7.—In a 58-year-old female with cardiac disease a cholecystectomy, done for chronic cholecystitis and cholelithiasis, was followed in the succeeding 5 years by increasingly frequent recurrent attacks of chills and fever, agonizing right hypochondriac pain with vomiting and jaundice, with clay-colored stools and highly colored urine.

The physical examination revealed a groaning, dyspneic, cyanotic, icteric person. The heart was not enlarged to percussion; the sounds were fair and the pulmonic sound was louder than the aortic. The cardiac rate was, however, totally irregular. The lungs were clear. The abdomen was obese, distended, rigid on the right side with tenderness in the right hypochondrium and epigastrium; and the liver was enlarged.

A severe chill with temperature of 105° F., cyanosis and semicoma intervened quickly and the patient died 9 hours after admission in cardiac failure. No laboratory work-up was possible.

The postmortem examination showed cholelithiasis, stenosis of the bile duct, acute and chronic suppurative cholangitis and hepatitis; toxic form of nephritis; splenomegaly and acute splenitis; chronic pancreatitis; diffuse fibrillary myocarditis and atheroma of the aorta.

This case presented a long-standing incomplete common duct obstruction with infection in the biliary radicals. Drainage through the common duct was at first sufficient to take care of the infection; but finally the drainage became incomplete and the infection then

overwhelmed the hepatic cells, producing liver insufficiency. Nevertheless, the immediate termination was a cardiac phenomenon, based upon an old endomyocardial lesion, and fatally exacerbated by the overwhelming infection.

Among cardiologists, the deleterious effect of a focus of infection upon cardiac lesions is so well known either as an inciting or contributory agent that a cardiac lesion has at times been the deciding factor in determining operation upon the biliary tract apparatus. Beneficial effects upon the cardiac condition have followed many of these operations. This should emphasize the advisability of early operative attention to gall bladder and liver conditions.

Evidence of severe renal damage was also present; this completes the clinical picture of the hepatorenal syndrome; and there is no doubt that, had the patient continued existence, the terminal phenomena would have been those of renal insufficiency.

Case 8.—In a 48-year-old man there was a history of a long-continued dyspepsia and episodes of epigastric pain associated with vomiting, light-colored stools, jaundice and latterly with chills and high fever. The impression given by the present 7-day-old episode was that the jaundice was of an obstructive nature with a superimposed cholangitic infection.

Physical examination revealed an acutely ill, icteric, cyanotic, white male. The lungs were clear except for an occasional sibilant râle. The heart had a soft blowing systolic murmur at the apex. There was rigidity of the upper rectus muscle with exquisite tenderness in the epigastrium. The liver was slightly enlarged.

The laboratory studies showed the following: hemoglobin, 58%; red blood cells, 4,600,000; white blood cells, 10,900; neutrophils, 70%; blood sugar, 101.5 mg.; blood urea, 13.4 mg.; creatinine, 1.41 mg.; cholesterol, 109.9; esters, 59%; Van den Bergh, direct 28.1 units; phenolsulphonephthalein, 10% in 2 hours; stools negative for blood; clay-colored; stomach analysis: free acid 20, total 44, no bile; bleeding time, 2 minutes and coagulation time, 4 minutes; urine, bile present.

The original impression, *i. e.*, obstruction plus infection, was confirmed. There was continued oliguria despite a satisfactory intake, but there was no azotemia, even though there was only 10% excretion of phenolsulphonephthalein in 2 hours.

It was not possible to prepare the patient suitably for operation and the symptoms continued. On the seventh day after admission he developed substernal oppression, a choking feeling, a fear of impending death, weakness, a totally irregular heart rhythm, and electrocardiographic evidence of auricular fibrillation with frequent ventricular extrasystoles. The general condition rapidly became critical, and exitus followed shortly thereafter.

The postmortem findings were: jaundice, ascites, nutmeg liver, congested fibrotic spleen, chronic peritonitis, chronic pleuritis, healed apical tuberculosis, contracted edematous gall bladder, dilated common duct, subepicardial, subendocardial and intramural hemorrhages; lymphoid hyperplasia.

This case presents a long-standing gall bladder disease with the sudden intervention of obstructive jaundice and cholangitis. There undoubtedly was some renal impairment present but the immediate terminal picture was a cardiovascular collapse, suggestive of sudden coronary occlusion.

Discussion. This series of biologic events has its inception in the biliary environment and begins usually before the fortieth year of life. In the initial primary stage of this disease, the process, for practical purposes, is limited to the gall bladder. The important facts that clinical experience has demonstrated are that in this stage the disease occurs in younger subjects, the general health is good, there are no complicating factors anywhere else in the body, the results of surgery are excellent, and the mortality is very small. These facts are true when the disease is brought under control at a fairly early period of its development, when the patients are under forty years of age and when preliminary medical treatment has not been unnecessarily prolonged.

If unchecked, the further progression of the disease occurs slowly and frequently extends over a span of life up to 20 and more years. The consequences occur most commonly in the fifth and sixth decades of life. Infection enters the picture sooner or later; then the process spreads upwards through the biliary tract; and presently, various forms and degrees of obstructive jaundice follow with secondary effects in the kidney. If reversal of the process and especially of its dangerous component, jaundice, is not promptly accomplished, a whole series of potentially more dangerous consequences develop, characterized by destruction of the liver parenchyma, secondary degenerative destructive changes in the kidney and anatomic changes in other organs which are commonly irreversible forerunners of a rapid and fatal termination.

The renal changes are often more marked than those in the liver; they often dominate all the other manifestations; and the terminal picture is that of "uremic poisoning," so that the renal picture may be taken as a measure of the severity of the entire disease. Nevertheless, the apparent rapidity of the terminal stage cannot alone be accounted for by the renal damage. Pathologic changes occur and coëxist in other important organs which destroy the ability of the individual to withstand the damage of the combination of primary liver and secondary kidney disease, with or without the traumatic insult of any necessary operation. In a generic way these include: changes in metabolism, notably obesity, degenerative changes in the myocardium and more or less acute closures in the coronary vascular circulation; profound disturbances in less acute closures in the coronary vascular circulation; profound disturbances in the hemopoietic system resembling a blood dyscrasia; and resultant toxemic disintegrating manifestations in the central nervous system.

Obesity. In the above series of cases, 70% of the women and 37% of the men were definitely obese. The association holds special relationship and importance to women, possibly because of the child-bearing function and consequent metabolic disturbances in

the lipoid (cholesterol) substances. In any case, practical clinical experience teaches the marked decrease in capability of resistance to infection, and to any form of operative insult.

Glycosuria. Glycosuria is an important complication of gall bladder disease in patients above 40 years of age. It is important to distinguish the group with associated pancreatic disease and the group with the ordinary forms of diabetes. With modern methods of treatment, glycosuria does not appear any more an important factor in the outcome of surgery for gall bladder disease.

Cardiac Disease. In preoperative electrocardiographic studies evidences of old coronary artery closures and of myocardial infarction are rather common. The latter should not be a necessary deterrent to surgical intervention, as with good care, the proper form of anesthesia and a rapidly performed operation, the great majority of the patients do well.

Cardiovascular collapse on a myocardial basis is a frequent terminal event. This usually occurs in those cases in which gall bladder disease and mild cholangitis have been present for a long time. The cardiac symptoms we have observed have been disturbances of rhythm with central and peripheral collapse.

Cardiac disease of this type is, generally speaking, a coincidental development during the years of elaboration of the entire gall bladder-liver-kidney sequence. And although, possibly, at the beginning, the heart lesion and the biliary tract lesion are independently derived, it is a clinical fact that sooner or later the two become interrelated. Universal experience has taught the lesson that any form of surgery, and especially biliary tract surgery, had better be practised before this complication appears, because cardiac disease contributes to and increases the mortality of operation to a large extent.

Acute coronary artery closures are much less commonly seen after operation upon these patients. They carry even a greater risk than under ordinary conditions.

The possibility of adequate preparation of the cardiac factor so that patients can overcome the added trauma of operation is undoubtedly related to the reserve powers of the individual heart. At the present writing this reserve cannot be estimated at all accurately for clinical purposes. Then the question of operative interference is a very difficult one to decide, frequently because of the impossibility of judging the operative risk. Nevertheless, operative intervention is imperative when any jaundice is present.

Hematologic Complications. The association of chronic liver disease, cirrhosis of the liver, and the blood picture of a macrocytic anemia is quite well established. In chronic disease of the liver there results a failure of storage of the factor necessary for the maturation of the red cells. Greene[3] has pointed out that this fac-

tor is present in acute yellow atrophy. None of our cases presented the blood picture of a macrocytic anemia, but hypochromic anemias were quite common. The unusual blood picture of Case 5 was probably not the result of an absence of some hemopoietic element from the liver, but rather the result of hepatic toxemia. I have had other similar experiences. I have observed, also, that many cases of hepatic insufficiency presented leukopenia, and 1 case presented thrombopenia. Hence depression in, or destruction of, the formed elements of the blood stream is probably another manifestation of hepatic insufficiency.

Symptoms Referable to the Central Nervous System. There is no pathologic evidence of any cerebral changes; but the presence of marked cerebral symptoms cannot always be explained on the basis of renal failure or the presence of any other abnormality which is commonly associated with them.

Relation to the Hepatorenal Syndrome. The association of hepatic and renal disease following primary gall bladder disease is only one of the many mechanisms of the much discussed "hepatorenal syndrome." In clinical medical and surgical practice there is widespread distribution of hepatorenal symptoms with or without lesions. One cannot escape the conclusion that the association of hepatic and renal pathologic conditions is necessarily frequent, because of the extraordinary biologic and functional intimacy of both of these extremely important organs. It seems that the two essential anatomic factors in this association do not occur in every case in the same intensity and proportion. Once this train of functional and anatomic disturbances begins, however, other factors come into play, such as fever, shock, autolysis of tissue, anoxemia, anhydremia, and azotemia, and the primary injury is enormously accentuated. The difference in the symptoms, in the suddenness and dramatic effect of the terminal clinical manifestations and in the rapid culmination in death seem to have most important relations to these various diverse, yet interlocking factors.

Conclusions. The great danger of withholding adequate treatment in this group of cases until irreversible changes occur is well shown by these individual clinical experiences. The lesson must be thoroughly learned that energetic treatment is necessary as soon after the inception of this pathologic process as is possible, when the lesion is limited to the gall bladder and biliary tract environment in order to obviate any possibility of the occurrence of any of the severe and dangerous manifestations which occur in the further biologic development of this disease and in order to eliminate the extra hazard which the presence of important cardiac and other associated lesions carry. The most important objects to be accomplished by surgery are: 1, the thorough removal of any focus of infection; and 2, the thorough removal of any obstruction to the unhindered outflow of bile into the intestine.

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AGNOGENIC CONGENITAL CLUBBING OF THE FINGERS AND TOES.

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Clubbing of the fingers and toes has been recognized since the time of Hippocrates as a manifestation of certain forms of intrathoracic disease. In 1889 von Bamberger[1] described the general thickening and sclerosis of the long bones which is frequently associated with clubbing. The following year Marie[8] unaware of Bamberger's work gave a full description of this syndrome and suggested the name "secondary hypertrophic pulmonary osteoarthropathy." Since that time there have been numerous studies and case reports most notably those of Locke[7] in 1915 and 1920 in which the literature was reviewed and brought up to date. There has been little information added up to the present time, except the term "acropachy" (thick extremity) has been suggested to designate the clubbing of the fingers and toes.

Hypertrophic osteo-arthropathy may be defined as a disease, usually secondary, occurring in the course of various chronic conditions, characterized by a general and symmetrical hypertrophy of the distal phalanges with resulting clubbing (acropachy), frequently accompanied by enlargement of some of the other bones in the hands and feet or by hypertrophy of the bones of the forearm and legs, and in the late stages, by involvement of the joints. Clubbing may be present without any bone changes and in some cases well marked osteo-arthropathy occurs without the characteristic clubbing. These variations have aroused a great deal of controversy whether or not these two conditions were related or independent but the evidence seems to favor the opinion that the two conditions are identical and part of the same disease process.

Three clinical types of the disease have been described by Sternberg:[11] 1, clubbing of the fingers and toes without changes in the long bones; 2, a combination of clubbing and painful thickening of the long bones, especially in the forearms and legs as described by von Bamberger; and, 3, an advanced stage in which there is conspicuous general and painful deformity and the primary disease is overshadowed by the severity of the osteo-arthropathy originally described by Marie.

It is well recognized that the changes in the digits and skeleton are nearly always secondary to some primary disease in the lungs, heart, liver or some other part of the body, suppurative pulmonary disease being most frequently the cause. This secondary form of the disease is well recognized but the mechanism of production of the changes is not known as yet. In certain rare instances clubbing of the digits with or without bone changes occurs in individuals in whom no apparent cause can be found by any clinical or laboratory methods. Some of these cases are familial and some congenital.

FIG. 1.—Hand showing marked clubbing.

Witherspoon[14] in 1936 reviewed the literature on congenital and familial clubbing, finding reports of 14 instances in addition to his case. In the congenital or familial type there is rarely progression from clubbing alone to the hypertrophic osteo-arthropathic type. This latter type is quite uncommon as Locke was able to collect only 5 instances from the literature in 1915; since that time H. M. Thomas, Jr.[13] has added one following a thyroidectomy, and Hollar and Agnor[5] have reported another in a negro male, aged 21. The case reported here is of interest because it portrays an instance in which there is clubbing of the digits of unknown cause associated with mild periosteal hypertrophy and occasional arthritic pain. This feature makes classification difficult; it probably represents mild or slowly progressive congenital chronic osteo-arthropathy.

Case Report. G. E., colored male, aged 22, was admitted to the York Hospital November 19, 1940, and discharged November 27, 1940. This

patient's condition was discovered in a routine health examination for the selective service. He has had clubbed fingers and toes as long as he can remember and has always enjoyed good health. He has never had any serious illnesses or operations except a tonsillectomy in 1926 from which he had an uneventful recovery. In 1935 he was given a routine tuberculin test to which he reacted. A Roentgen ray of the chest was taken at that time which revealed no lesion. He states that his father has the same condition but knows definitely that his brother does not; unfortunately, the father resides in another state and cannot be reached. The patient is a rather intelligent negro and I believe his observations may be correct. There are no other siblings. Family history is otherwise irrelevant. His subsequent history is completely normal except occasional pain in each

FIG. 2.—Clubbed fingers showing absence of spatulation.

knee after a period of excessive exertion. During his stay in the hospital his temperature, pulse and respiratory rates were normal. Other than the marked clubbing of all the fingers and toes the physical examination was not remarkable. There was a bulbous enlargement of the finger tips and toe tips, double curvature of the nails, and a considerable degree of cyanosis of the nail bed.

Urine examinations were normal. Hematologic studies were normal with the exception of a mild degree of anemia, the Hb. being 13 gm. and the R.B.C. 4.1 million. The blood Kahn text was negative. Electrocardiographic tracings were normal. The procholon time was 14 sec., the ether time 6 sec., and the venous pressure was 15 cm. of water.

Roentgen studies of the sinuses and chest were not remarkable. Lipiodol injection into the tracheobronchial tree revealed no abnormalities; the long bones were normal except mild periosteal thickening of each tibia.

Etiology. The theories concerning the production of secondary clubbing are numerous and exceedingly diverse, ranging from capillary hyperemia, defective oxygenation, circulating toxins, certain nervous diseases, syphilis, tuberculosis, avitaminosis to amyloid degeneration. No one mechanism is able to explain the changes without serious objection. It is not hard to understand

FIG. 3.—Bones of the leg showing a mild degree of periosteal hypertrophy.

that the method of production of primary or congenital clubbing is even more indefinite and hazy than the secondary form. At the present time there is no adequate explanation for the production of either form.

The gross appearance of clubbing is easily recognized and needs no further description. However, there has been no general agreement of the microscopic findings in the few cases studied. Campbell[3] states that there is an edematous condition of the tissues lying

between the nail bed and the bone. Freytag[4] reported dilatation of the capillary loops in the bed with engorgement of the interpapillary processes, but found no alteration in the skin, nerve changes or endarteritis obliterans. Therese[12] noted hypertrophy of the horny layer, papillæ and the connective tissue of the derma. Buzzard[2] noted an excess of subcutaneous fat, Schirmer[10] found a tissue resembling embryonic mucoid and Thomas[13] reported marked dilatation of the venous and marked tortuosity of the arterial capillaries of the nail bed.

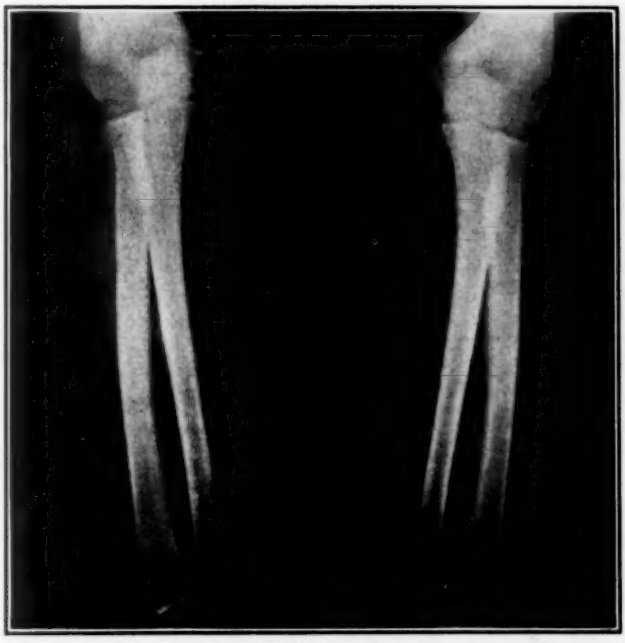

FIG. 4.—Bones of the forearm showing a very slight periosteal hypertrophy.

As the change in simple clubbing of the digits is usually confined to the soft parts there are no changes in a Roentgen examination of the digits in most cases. In a few cases there has been definite proliferation of the bone in the distal phalanges and Ragins and Freilich[9] Kayne,[6] and Witherspoon[14] have reported a definite splaying of the distal phalanges in the familial type of clubbing. When there are changes of the long bones the hypertrophy of the bones in the terminal digits is more common.

Summary. 1. A case is reported of clubbing of the digits of unknown etiology—probably congenital and familial.

2. This instance represents a border-line situation between acropachy and chronic osteo-arthropathy.

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THE STANDARDIZATION OF THE CONGO RED TEST FOR AMYLOIDOSIS.

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The Congo red test has been used very extensively during the past few years to determine the presence of amyloidosis, especially in those patients who have been suffering from chronic pulmonary tuberculosis. At this hospital 22% of the cases which have come to autopsy revealed amyloidosis.

The test in the great majority of cases has proved very useful as a diagnostic procedure, although in many instances we have found it to be inadequate. The discrepancies occurred in those cases where the blood serum removed 4 minutes after the intravenous injection of Congo red was either too light or too dark in color, thus rendering the specimen inadequate for use as a standard for colorimetric comparison with the blood serum removed one hour after injection.

An attempt was made to investigate the reasons for such discrepancies and to arrive at a standard and uniform test.

It was found that in all cases where the greatest variations in color intensity occurred the body weights of the patients were either much greater or much less than 100 pounds. The 4-minute specimens were too light in color when the body weights ranged between 140 and 190 pounds. Conversely, when the body weights ranged between 40 and 70 pounds, the 4-minute specimens showed a strong color intensity.

The obvious factor involved then seemed to be the relationship between the amount of dye used and the body weight. In most institutions 10 cc. of a 1% solution of the dye are given to all patients regardless of body weight (according to Bennhold).[1]

Keith, Rowntree and Geraghty,[3] in determining blood volume with vital red, injected 1 cc. of a 1% solution of the dye per 5 kilos of body weight.

Osgood and Haskins,[6] in giving the method for the Congo red test for amyloidosis, quote the procedure of Keith, Rowntree and Geraghty as modified by Harris,[2] for the estimation of blood volume. They state that one-fourth the body weight in kilos of a 1.5% solution of Congo red should be injected. This appears to be the first attempt at a standardization of the test for amyloidosis, since it takes into consideration both the blood volume and the body weight.

We have found at this hospital that the injection of 1 cc. of a 1% aqueous solution of the dye per 10 pounds of body weight gave standard specimens which closely approximated each other in color intensity and which could be used for colorimetric determinations. Any greater amount of dye, when used expressly as a test for the presence of amyloidosis, seems superfluous.

The standardized test given here includes a modification of the original Bennhold technique in the treatment of the blood prior to colorimetric comparison. This is the acetone extraction procedure devised by one of us[8] to eliminate any hemoglobin which might be present due to hemolysis.

Method. Inject 1 cc. of a 1% aqueous solution of Congo red per 10 pounds of body weight intravenously. At the end of exactly 4 minutes, and then 1 hour, after the injection, obtain blood specimens of 10 cc. each and place them into clean, dry test tubes. Allow the bloods to clot and retract and then centrifuge them at a moderate speed for 10 minutes. Aspirate off the clear sera and place them into graduated centrifuge tubes. Add acetone equal to the volume of serum in each tube and shake them well. Centrifuge the tubes for 10 minutes at a moderate speed. Pour off the supernatant fluids and place them into micro cups of a colorimeter to be compared. Set the 4-minute specimen at 20 mm. and read the 1-hour specimen.

Calculation:

$$100 - \left[\frac{\text{Reading of 4-minute specimen}}{\text{Reading of 1 hour specimen}} \times 100 \right] = \text{per cent absorption}$$

For example: The 4-minute specimen is set at 20 mm. in the colorimeter. The 1-hour specimen reads 25. Therefore the per cent absorption of the dye is 20.

To prove the advantage of the standard test over the usual technique of using 10 cc. of dye for all patients, we performed a series of tests using known amyloid and non-amyloid cases. In one series of the non-amyloid group we performed tests with patients whose body weights varied greatly, each receiving 10 cc. of dye. As shown in Table 1 the 4-minute specimens varied markedly, the

difference between them ranging from 15 to 75%. In some instances, the 4-minute specimens were practically devoid of dye, making comparisons with the 1-hour specimens impossible. These cases typify the results obtained in a large hospital where many Congo red tests are performed and where 10 cc. of dye are injected into all patients.

TABLE 1.—NON-AMYLOID GROUP (50–175 POUNDS)—10 CC. DYE.

Case.	Body weight (pounds).	% dye absorption in 1 hr., using 4-min. specimen as standard.*	Suitability of 4-min. specimen as standard.	Comparisons between 4-min. specimens of different Congo red tests chosen at random. Cases.	% variation.
1	76	55	Too dark	1 *vs.* 2	= 15
2	51.5	20	Too dark	1 *vs.* 3	= 45
3	153	50	Too light	2 *vs.* 5	= 60
4	170	No comparison possible	Too light	5 *vs.* 6	= 70
5	140	55	Too light	5 *vs.* 7	= 75
6	59.5	25	Too dark	2 *vs.* 3	= 68
7	63.8	30	Too dark	8 *vs.* 10	= 40
8	80	40	Too dark	1 *vs.* 10	= 65
9	167.8	No comparison possible	Too light	2 *vs.* 10	= 60
10	147	60	Too light	7 *vs.* 10	= 55
11	64.5	25	Too dark	11 *vs.* 14	= 60
12	51.8	20	Too dark	11 *vs.* 12	= 20
13	162	No comparison possible	Too light	12 *vs.* 14	= 55
14	142.5	60	Too light	10 *vs.* 11	= 65
15	171	No comparison possible	Too light	8 *vs.* 14	= 45
16	59	15	Too dark	16 *vs.* 17	= 72
17	142	60	Too light	16 *vs.* 19	= 10
18	163	No comparison possible	Too light	17 *vs.* 19	= 58
19	51	20	Too dark	17 *vs.* 20	= 60
20	60	25	Too dark	19 *vs.* 20	= 20
21	152	70	Too light	20 *vs.* 21	= 55
22	56	30	Too dark	21 *vs.* 22	= 60
23	70.5	35	Too dark	21 *vs.* 23	= 55
24	147.5	65	Too light	23 *vs.* 24	= 70
25	155.5	60	Too light	24 *vs.* 25	= 22

* 4-min. specimen represents zero absorption

Another group of non-amyloid patients was chosen with nearly the same body weights. Each of these patients received 10 cc. of dye. In this group all 4-minute specimens were satisfactory as standards and no marked deviations in them were found. The 4-minute specimens varied between 2 and 12%. The results of these tests can be seen in Table 2.

Not only did 4-minute specimens of patients whose body weights were in the vicinity of 100 pounds check closely, but also those of patients of greatly varying body weights, when they were given 1 cc. of dye per 10 pounds of body weight.

A group of amyloid patients was given injections of the dye according to the standard method outlined above. The criteria for the presence of amyloidosis in this group consisted of previous Congo red tests, which gave results ranging from 90 to 100% absorption, and clinical manifestations. These latter included enlarged, palpable livers and spleens and varying degrees of albumin-

uria. In previous works Lipstein and Auerbach[5] and Lipstein[4] have demonstrated the close correlation between the Congo red tests and clinical and postmortem findings. With few exceptions, amyloidosis was found to be present in greater or lesser degree in all cases having dye absorptions between 90 and 100%.

TABLE 2.—NON-AMYLOID GROUP (95–105 POUNDS)—10 CC. DYE.

Case.	Body weight (pounds).	% dye absorption in 1 hr., using 4-min. specimen as standard.*	Suitability of 4-min. specimen as standard.	Comparisons between 4-min. specimens of different Congo red tests chosen at random.		
				Cases.		% variation.
1	101	60	4+	1 *vs.* 2	=	8
2	95.5	75	4+	2 *vs.* 3	=	10
3	104.8	50	3+	3 *vs.* 4	=	8
4	99.5	40	4+	4 *vs.* 5	=	12
5	102	45	3+	1 *vs.* 5	=	5
6	102.8	30	4+	5 *vs.* 6	=	2
7	104.5	40	3+	6 *vs.* 7	=	6
8	98.5	50	4+	7 *vs.* 8	=	9
9	100.8	35	4+	8 *vs.* 9	=	3
10	95.5	55	4+	8 *vs.* 10	=	2
11	98	25	4+	10 *vs.* 11	=	8
12	96.8	35	4+	11 *vs.* 12	=	3
13	101.5	45	4+	12 *vs.* 13	=	5
14	103	50	3+	13 *vs.* 14	=	10
15	99.8	45	4+	14 *vs.* 15	=	10
16	98.3	35	4+	15 *vs.* 16	=	10
17	101.3	30	4+	15 *vs.* 17	=	6
18	104	35	4+	16 *vs.* 18	=	5
19	101.5	45	4+	17 *vs.* 19	=	5
20	102.3	55	4+	19 *vs.* 20	=	8
21	97.3	50	4+	20 *vs.* 21	=	10
22	100.3	40	4+	21 *vs.* 22	=	12
23	101.5	35	4+	22 *vs.* 23	=	10
24	104.3	45	3+	23 *vs.* 24	=	10
25	102.3	55	4+	24 *vs.* 25	=	8

4+ = very good 4-min. specimen; 3+ = good 4-min. specimen.
* 4-min. specimen represents zero absorption.

In this group, which consisted of 42 cases, we again obtained values ranging from 90 to 100% absorption. The absorption in the majority of cases was 100%. No case was considered as 100% absorption unless the 4-minute specimen showed a good color intensity comparable to that obtained in the non-amyloid group.

The 4-minute specimens were satisfactory as standards with the exception of 11 cases. In each of these cases the 4-minute specimen was too light in color to be relied upon as a standard even though the dye was given in proportion to body weight. This led us to investigate the 11 cases further in order to obtain a standard test which would be as free from error as possible in the diagnosis of amyloidosis.

After a period of several months Congo red tests were repeated on the 11 cases in addition to most of the other amyloid cases (24) and on 60 additional non-amyloid cases. We adopted the procedure of obtaining three blood specimens, namely, 2 minutes, 4 minutes and

then 1 hour, after the injection of the dye, which was again given according to body weight. The reason for taking the additional blood specimen (2-minute) was based on our assumption that in the presence of widespread amyloidosis practically all of the dye was absorbed in less than 4 minutes.

The results of these experiments attributed to the adoption of our final standard test. In all 11 cases, as well as in the other amyloid cases, the 4-minute specimens were duplicates of what we had obtained previously. The 2-minute specimens, however, showed excellent color intensities. This gave us the desired information concerning the validity of the test as a diagnostic aid. Whereas previously these tests were reported as containing an insufficient amount of dye, they were now reported as 90 to 100% absorption with the assurance that a proper amount of dye was introduced into the vein. The differences between the 2-minute and the 4-minute specimens were marked. In some cases differences of as much as 75% were noted. Table 3 serves to illustrate this point.

TABLE 3.—AMYLOID GROUP—USING STANDARD TEST.

Case.	% dye absorption in 1 hr., using 2-min. specimen as standard.*	Comparisons between 2-min. and 4-min. specimens on each patient (% variation).
1	100	40
2	100	25
3	100	70
4	100	20
5	100	25
6	100	55
7	90	75
8	100	70
9	95	60
10	100	40
11	100	25
12	100	35
13	100	45
14	100	50
15	100	45
16	100	20
17	100	70
18	100	75
19	100	55
20	100	25
21	100	50
22	100	50
23	100	45
24	95	45
25	100	40
26	100	45
27	100	65
28	100	55
29	100	45
30	100	50
31	100	60
32	100	50
33	100	45
34	95	55
35	100	65

* 2-min. specimen represents zero absorption.

The differences between the 2-minute and 4-minute specimens in the 60 non-amyloid cases were not great. Table 4 shows that the greatest single difference in this group was 15%, with a mean deviation of 8%. The per cent of dye absorption of these cases was still within normal limits, that is, less than 90%.

The validity of this entire study is borne out by the fact that 21 of the 42 "amyloid" cases have since come to autopsy and each revealed amyloidosis of greater or lesser degree. Also, of the total number of non-amyloid cases under study (110), 20 cases have come to autopsy and only one revealed a moderate degree of amyloidosis. The Congo red test on this case was performed 4½ months prior to death and yielded an absorption of 65%. It is entirely probable that amyloidosis had developed during this interim.

We concluded that the 4-minute specimen was inadequate as a standard where widespread amyloidosis was present. In its place we introduced the 2-minute specimen to serve as a standard for colorimetric comparison. In the case of complete absorption of the dye in the 1-hour period the 2-minute specimen serves as a standard, not from the point of view of comparison with the 1-hour specimen (which is devoid of dye), but to demonstrate to the clinician that a sufficient amount of dye was originally introduced into the vein. Since there were only slight differences between the 2-minute and the 4-minute specimens in normal subjects it does not matter materially that the 2-minute specimen is made a standard for colorimetric comparison.

Since the standard test described necessitates a larger amount of dye than most frequently used, it may be of interest here to mention a word about the toxicity of the dye. Richardson and Dillon[7] have recently studied the toxic effects of intravenous injections of Congo red in animals and have found a high tolerance for the dye by cats, rabbits, pigeons and rats. They state that "the highest tolerated single doses in mgs. per kilo body weight were as follows; pigeons, 100; rats, 140; rabbits, 200; cats, 100." This demonstrates the wide margin of safety in using the dye intravenously.

Summary and Conclusions. 1. A standardized method for the Congo red test for amyloidosis is presented.

2. The dye is administered according to body weight. It was found that 1 cc. of a 1% aqueous solution of the dye per 10 pounds of body weight yielded more accurate tests than the fixed amount customarily used.

3. Tests were performed on amyloid and non-amyloid patients, using both the usual technique of injecting 10 cc. of dye regardless of body weight and the standardized method.

4. In one non-amyloid group patients were selected whose body weights were nearly the same (range between 95 and 105 pounds) and in the other those whose body weights varied considerably (range between 50 and 175 pounds). The former group showed consistently reliable 4-minute specimens, while the latter gave

TABLE 4.—NON-AMYLOID GROUP—USING STANDARD TEST.

Case.	% dye absorption in 1 hr., using 2-min. specimen as standard.*	Comparisons between 2-min. and 4-min. specimens on each patient (% variation).
1	30	5
2	35	5
3	25	8
4	40	10
5	65	8
6	50	6
7	55	8
8	40	5
9	45	15
10	40	5
11	65	10
12	70	6
13	75	5
14	30	5
15	35	8
16	20	7
17	35	10
18	45	10
19	45	5
20	40	6
21	65	5
22	60	5
23	50	8
24	55	5
25	45	10
26	30	10
27	25	10
28	35	5
29	60	10
30	30	8
31	35	10
32	50	5
33	55	5
34	60	10
35	65	12
36	65	15
37	60	5
38	55	10
39	50	10
40	55	8
41	40	10
42	35	8
43	25	5
44	20	5
45	25	10
46	60	8
47	65	5
48	60	8
49	60	10
50	50	10
51	55	8
52	50	5
53	55	8
54	65	9
55	60	10
56	55	8
57	65	8
58	70	10
59	75	12
60	65	8

* 2-min. specimen represents zero absorption.

4-minute specimens which differed by as much as 75%. In some cases the per cent absorption could not be computed because of insufficient dye in the 4-minute specimens.

5. In the amyloid group 90 to 100% absorption was a consistent finding. This is in so close correlation with previous work that such results must be obtained to indicate amyloidosis. In all but 11 cases the 4-minute specimens contained sufficient dye to be considered as appropriate standards.

6. These 11 cases were investigated further along with 24 of the other amyloid cases and it was found expedient to draw a 2-minute specimen in addition to the 4-minute and 1-hour specimens. A group of 60 non-amyloid cases was chosen as controls. In all of the amyloid cases, the 2-minute specimens showed good color intensity and the differences in color between them and the 4-minute specimens were marked (as high as 75%). There were only slight differences in color intensity between the 2-minute and 4-minute specimens in the non-amyloid group, the highest per cent variation being 15.

7. The 2-minute specimen was adopted as the colorimetric standard in place of the 4-minute specimen.

8. Since the inception of this study 21 of the 42 amyloid patients have come to autopsy and each revealed amyloidosis of greater or lesser degree. Twenty of the non-amyloid patients have come to autopsy and only one case revealed a moderate degree of amyloidosis.

9. The standardized method has improved the accuracy and reliability of the test as a diagnostic aid.

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THE EFFECT OF DIET AND MEALS ON THE MAXIMUM UREA CLEARANCE.*

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Among tests of kidney function the urea clearance of Möller, McIntosh and Van Slyke[11] holds a deservedly popular place. Its

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precision in borderline cases, however, is impaired by a number of factors, aside from the state of the kidneys, which have been reported to effect its values. The influence of two of these, the previous diet, and meals, are the subject of this study.

In dogs, Shannon, Jolliffe, and Smith[16] found the fasting urea clearance on a meat diet to be as much as double that on a cracker diet. Pitts[13] found that a low protein meal had little effect, while meat produced a gradual and prolonged rise in clearances, whether the dogs had been on a basal or meat diet. Glycine, glycylglycine, and alanine had an effect similar to meat. Since the clearances were also increased by injection of thyroxin or phloridzin, Pitts concluded that protein metabolism as such, whether endogenous or exogenous, is responsible for the increase in renal function. Because the urea/xylose clearance ratio remained quite constant, the effect is better explained by an increased renal blood flow rather than by any change in the mechanism of urea excretion. Van Slyke, Rhoads, Heller, and Alving[19] reached the same conclusion, and noted that administration of urea gave no change in the clearance.

In normal man,[3,7] the changes are not so great as in the dog, clearances on low protein diets being usually about 30% less than those on more liberal protein intakes. But the change in clearance does not seem to be proportional to the protein intake, for the reduction was no greater on a 9- than on a 40-gm. protein diet, and ingestion of 280 gm. daily did not raise it above the level found on a 100-gm. diet.

Because of the probable effect of meals, it is usually customary to determine the urea clearance in the fasting state. However, MacKay[9] showed that an ordinary breakfast had no effect on the standard clearance. If the same holds true for maximum clearance it would simplify the technique of the test.

The present experiments aimed to determine whether the urea clearance was proportional to the protein intake, or whether there was a critical intake at which it increased, and whether this corresponded with any change in basal metabolic rate or cardiac output. In addition, observations have been made of the effect of large and small meals on maximum clearance with both low and high protein diets.

Methods. All determinations were made in duplicate. Urine urea nitrogen was determined by the manometric urease method of Van Slyke.[12] Whole blood urea nitrogen was estimated by the hypobromite method of Van Slyke and Kugel[18] or by the aëration and titration method of Cullen and Van Slyke.[12] Because the hypobromite method yields only 95% of the urea nitrogen and a variable amount from amino-acids, necessitating the use of an empirical correction, its reliability for low values seemed questionable. A series of determinations was therefore carried out by both methods on the same samples. The average difference in the two methods in 15 determinations on bloods containing 3 to 9 mg. urea nitrogen per 100 cc. was 0.36 mg. per 100 cc. There was no systematic difference; in 9 instances the hypobromite method gave the higher value, in 4 the lower.

In 8 comparisons on bloods containing above 10 mg. urea nitrogen per 100 cc. the average difference was 0.23 mg. per 100 cc. On the basis of this comparison, it was decided that the hypobromite method, even in the low range, gave results sufficiently accurate for the purpose of this study. The length of urine collection periods was usually 1 hour; with high urine flows occasionally 45 or 30 minutes. When there was any doubt concerning the ability to empty the bladder, the patient was catheterized. Except in studying the effect of meals, collections were made at an approximately constant diuresis or on a falling curve, and under basal conditions.

Inulin was determined in plasma and urine by the method of Corcoran and Page.[4] Cardiac output was estimated from intra-arterial pressure curves and pulse wave velocities by Bazett's[2] method. Total urine nitrogen was determined by micro-Kjeldahl.

Subject L, age 28, was observed on diets containing 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.4, 2.7 and 3.8 gm. of protein per kilo which furnished from 19 to 240 gm. of protein. The total caloric intake was kept approximately constant. Sufficient time was allowed on each diet for the establishment of nitrogen equilibrium, as indicated by total urinary nitrogen, before clearances were determined. Four to nine maximum clearances, each of ½ hour, were obtained under basal conditions. Blood was drawn at the beginning and end of the collections, and interpolated values used in the calculations. Estimations of the basal metabolic rate were made at each level of protein intake, of cardiac output on alternate diets, and of inulin clearance on the lowest and highest protein intake (see Table 1).

TABLE 1.—CHANGES IN MAXIMUM UREA CLEARANCE, BASAL METABOLISM, AND CARDIAC OUTPUT WITH DIETARY PROTEIN.

Subject L., age 28, height 163 cm., weight 64 kg.

Protein.		Mean fasting B.U.N., mg./100 cc.	Mean max. urea clearance, cc./min.	Mean inulin clearance, cc./min.	Urinary nitrogen, gm./24 hrs.	B.M.R., %.	Cardiac output, l./min.
Gm./kg.	Total.						
0.3	19	4.0	54.8	123	3.6	−14*	3.21
0.6	38	6.1	63.9	..	5.7	−21	
0.9	58	10.5	61.2	..	8.3	−13	
1.2	77	10.1	63.8	..	12.1	−18	
1.5	96	12.6	71.8	..	14.9	−15	3.36
1.8	115	12.9	68.6	..	17.3	−17	
2.4	150	17.1	75.3	144	22.5	−13	2.68
2.7	186	19.0	76.5	..	27.7		
3.6	230	17.9	77.0	..	35.3	−18	

* In spite of the persistently low basal metabolic rate, the subject showed no clinical or other laboratory evidence of hypothyroidism.

While there was considerable variation in the individual clearances, the mean clearance on each diet shows a significant correlation with the protein intake. There was no detectable change in basal metabolic rate, nor in basal cardiac output. Inulin clearance, assumed to represent the volume of glomerular filtrate, was somewhat greater on the higher protein diet. The urea/inulin clearance ratio was not significantly changed, being 0.45 on the low protein diet and 0.52 on the high.

Chart 1 shows a progressive increase in mean clearance from the lowest protein diet up to one containing about 100 gm. of protein. Diets containing more protein did not give any further increase in clearance. There is enough variation in the individual clearance periods to make the difference in means between on any two adjacent diets not statistically significant, nor is the difference between the mean on the 0.6 and 1.5 gm. per kilo diets significant. The

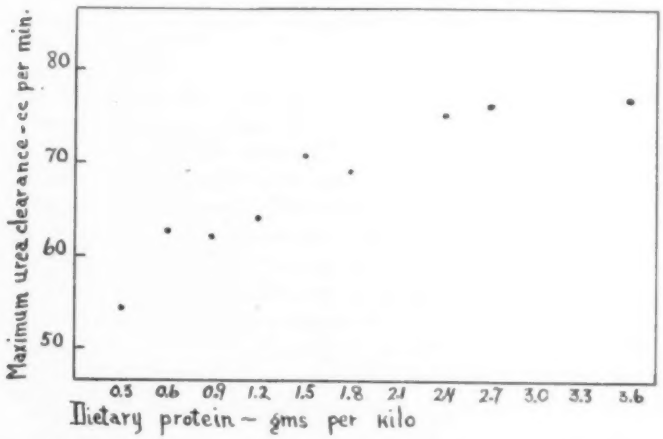

CHART 1.—Relation between dietary protein and mean fasting maximum urea clearance in Subject L.

difference between the mean clearance on the 0.3- and on the 1.5-gm. diets, 12.99 ± 3.79 cc. is significant according to Fisher's[5] test for t as well as the difference between the 0.6- and 2.4-gm. diets (11.50 ± 4.04). Taking all the points on the ascending part of the curve (0.3 to 2.1 gm./kg.) the correlation coefficient between protein intake and mean clearance is 0.860.

Similar, but less complete, studies were made on another subject, B, age 16, weight 64.4 kilo. On a diet containing 20 gm. protein (or 0.3 gm./kilo) his mean basal maximum urea clearance was 57.33 cc. per minute with a blood urea nitrogen of 5 mg. per 100 cc., while on a diet containing 40 gm. protein, or 0.6 gm. per kilo, his blood urea nitrogen rose to 7.5 mg. per 100 cc. and his mean clearance to 65.82 cc. per minute. The difference, 8.49 ± 3.38, is significant. In this subject, however, there was no further rise in clearances on a diet of 100 gm. or 1.5 gm. per kilo. This, however, is open to question for although he had been on the diet for 12 days, he was still not in nitrogen equilibrium. Mean inulin clearance rose significantly from 105 cc. per minute on the low diet to 130 cc. on the highest, while the urea/inulin ratio remained unchanged (0.54 and 0.49). As in the first subject, there was no increase in estimated basal metabolic rate or cardiac output.

These data raise two questions: what is the explanation of the increasing clearance with diets from 19 to 100 gm. of protein; and why does the clearance not continue to rise with higher diets?

The data on dogs are consistent with the belief that the increased clearances may be attributed to an increased renal bloodflow. The increased inulin clearance in these subjects are consistent with the same interpretation, provided the inulin extraction ratio remained constant. But since there was no measurable change in cardiac output or basal metabolism, the increased renal bloodflow may have been brought about by intrarenal vascular adjustments rather than by an increase in cardiac output. Some such mechanism is also suggested by the difference between the changes in clearance due to diet and those due to hyperthyroidism. Two patients with hyperthyroidism were studied before treatment and after recovery from thyroidectomy. In both, basal metabolic rate, cardiac output, and inulin and urea clearances fell after operation, but the fraction of the cardiac output represented by the inulin clearance was unchanged. The level of blood urea nitrogen in 1 patient was 7.6 mg. per 100 cc. before and 4.4 mg. per 100 cc. after operation, in the other 14.9 and 12.7. Both patients were receiving a diet containing 100 gm. protein when the clearances were determined. That is, in hyperthyroidism, the increased renal blood flow and clearances apparently are a reflection of the increased metabolism and cardiac output, while in normal subjects changes in metabolic rate and cardiac output could not be detected with alterations in diet. For while in a normal subject protein overfeeding for a number of days causes a cumulative increase in the specific dynamic action of protein, the effect lasts only so long as the food is being absorbed, and does not give an increase in the fasting metabolic rate.[13] Since these increased clearances were observed under basal conditions, they cannot be attributed to increased metabolism from the previous day's protein intake. Nor can the increased clearance on high protein diets be attributed to the elevated blood urea nitrogen. Möller, McIntosh, and Van Slyke,[11] and others have shown that raising the blood urea nitrogen from the normal range of 10 to 16 mg. per 100 cc. to two or three times as much by feeding urea had no effect on the clearance value. Cope,[3] however, pointed out that to obtain by urea administration the same blood changes that are produced by low and high protein diets, it would be necessary to administer urea to a subject in nitrogen equilibrium on a low protein diet. Data of Fowwether[6] suggested that under such conditions urea itself might be responsible for an increase in clearance. However, in Subject B while in nitrogen balance on a diet containing 19 gm. of protein with a fasting blood urea nitrogen of 6.2 mg. per 100 cc. neither the ingestion of 30 gm. of urea, which raised the blood level to 30.4, nor of 5 gm. every 4 hours for 2 days led to any increase in the maximum urea clearance. This seems to complete the evidence against urea.

The suggestion of Pitts[13] supported by the earlier work of Addis and Drury,[1] that the effect is due in some way to the amino-acids, remains. But the data give no hint whether this is mediated through renal vasodilatation, perchance more marked on the afferent glomerular arteriole, or by some other means. The constancy of the urea/inulin clearance ratio would seem to make any change in the reabsorption of urea unlikely.

With increasing protein diet, there is an increase in the fasting level of blood urea nitrogen (Chart 2). This also is progressive up

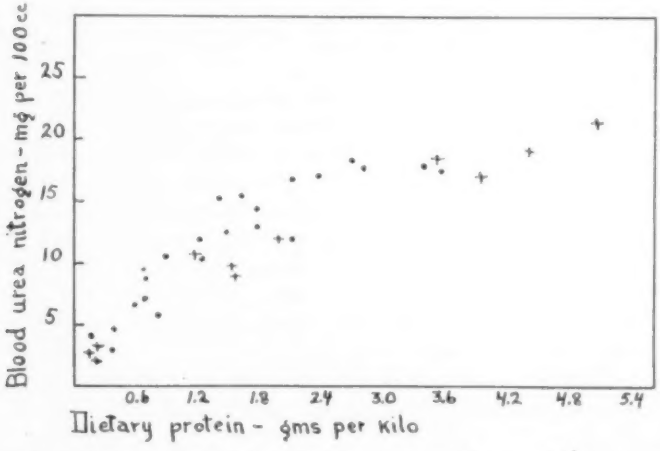

CHART 2.—Relation between dietary protein and fasting blood urea nitrogen in subjects in nitrogen equilibrium. Crosses from data of Goldring *et al.*

to about 2.8 gm. of protein per kilo, and then flattens out. This diet is also about that at which clearances stop increasing. Progressive retention on a high protein diet is prevented by increasing 24-hour urine volume rather than by increase in clearances. When allowed water as desired, Subject L (a notorious water drinker) had a 24-hour urine volume of 2000 to 2400 cc. on diets below 60 gm. protein, while it averaged 3920 cc. on a 114-gm. diet and over 4700 cc. on the highest diets. Two other subjects allowed water as desired had average urine volumes of 945 and 692 cc. per day on a diet containing 20 gm. of protein and 1690 and 1330 cc. on diets containing 100 gm. of protein. Price, Miller, and Hayman[14] also found consistently higher urine volumes on high protein diets. The effect of diuresis on nitrogen elimination, however, is not simple. The older literature quoted by Marshall[10] indicates an increased nitrogen elimination with diuresis, but it is well known that a subject in nitrogen equilibrium on low or moderately high protein diets excretes a constant amount of nitrogen in widely varying 24-hour volumes. The answer would seem to be in the fraction

of the 24 hours in which urine volume is above the augmentation limit. With a constant blood urea nitrogen an increase in urine volume to the augmentation limit increases urea excretion. Further increase has little or no effect, but an increase in the number of hours during which urea is excreted at a maximum rate increases the urea eliminated per day. This is born out by the fall in blood urea nitrogen during a series of clearances while fasting, in spite of the fact that the value of the clearance itself does not change.

TABLE 2.—CHANGES IN FASTING MAXIMUM UREA CLEARANCE WITH MODERATE ALTERATION IN PROTEIN INTAKE.

Subject.	Ht. Wt.	Protein, gm.	Mean B.U.N., mg./100 cc.	Mean clearance, cc./min.	Protein, gm.	Mean B.U.N., mg./100 cc.	Mean clearance, cc./min.
D	173.5 56.4	40	6.7	51.4	100	14.9	60.5
M	180.0 72.5	50	9.9	71.1	110	14.9	81.3
Br.	172.0 77.0	50	9.5	77.8	130	15.7	86.3
B	171.0 65.4	40	7.9	65.8	100	10.1	63.3
R	181.0 72.7	20	4.0	93.5	150	10.2	111.1
McC.	177.5 61.2	30	4.1	65.0	150	13.8	76.7

Six additional subjects have also been studied on two diets: in 4, the low protein diet contained 40 to 50 gm., while in the other 2, it was reduced to 20 and 30 gm. The mean blood urea nitrogen and clearances of these subjects are shown in Table 2. The first 4 had fasting blood urea nitrogens above 6 mg. per 100 cc. on the low protein diet, and while the mean clearances on the high diets are elevated, in none of the 4 is the difference significant. The other 2 subjects had fasting blood urea nitrogens of 4 and 4.1 mg. per 100 cc. on diets of 20 and 30 gm. of protein, and showed a significant increase in clearance on 150-gm. protein diets. It would seem that while man, like the dog, shows a decreased urea clearance on low protein diets, that this only becomes significant when the protein intake is markedly restricted, and that variations in protein intake of ordinary diets, from 40 gm. up, need not be considered in determining the urea clearance as a test of kidney function. Cope,[3] however, found that such changes in diet did make a difference in the standard clearance in nephritic subjects.

Chart 2 shows the relation between fasting blood urea nitrogen and protein intake in our data and that of Goldring, Razinsky, Greenblatt, and Cohen.[7]* In normal subjects the fasting blood urea nitrogen furnishes a fairly reliable index of the level of protein metabolism over the usual range of diet. Variations in diet are probably an important factor in the wide spread usually given for

* Dr. Goldring kindly furnished the weights of his subjects and has allowed us to use his data.

the "normal" blood urea nitrogen. Since this does not fall below 6 mg. per 100 cc. as a rule until the protein intake is below 0.6 gm. per kilo or about 40 gm., the possibility that low maximum clearances are due to a low protein intake can probably be disregarded if the fasting blood urea nitrogen is 6 mg. per 100 cc. or above.

The effects of meals on maximum clearances in subjects on low and high protein diets are shown in Table 3. On each diet, the subjects were given meals corresponding to that diet. On a 40-gm. diet, B's mean clearance averages slightly higher with meals, but the difference is not significant (P = 0.88. P is the probability that a difference between the means as great as or greater than that observed would not be obtained by the operation of chance alone). With the higher protein diets both B and L showed a significantly higher mean clearance with meals (P = >0.999 and >0.999). Other data on 3 individuals observed throughout the day with meals corresponding to 40- and 100-gm. diets also showed increases after meals, more marked as would be expected when larger amounts of protein were ingested. It was frequently noted that in spite of a constant fluid intake the urine volume diminished immediately after a meal, so that "standard" rather than "maximum" clearances were obtained. This probably reflects diversion of blood to the intestinal tract during the process of digestion with consequent diminution in renal blood flow. The variability of a series of clearances without meals, however, is just as great as when the subject is fed. The average coefficient of variation for clearances with meals was 11.4% and 9.5% fasting. Considering all our data, it seems likely that a meal containing 10 gm. or less of protein will not significantly affect the maximum urea clearance.

The effect of larger protein meals on maximum urea clearance contrasts with MacKay's[9] findings that meals are without effect on the "standard" clearance. MacKay's conclusion, however, was based on variations throughout the day in 4 subjects who received meals, without equal periods of observation fasting, and on 1 normal subject observed from 8 to 10 A.M. on 3 days with and 3 days without breakfast. No data are given on the amount of protein taken by this subject.

Table 4 shows the effect of a single large protein meal (114 and 109 gm.) on the clearances when the subject had been on low and high protein diets. On the low diet, there is little change for 6 hours and then a sudden sharp rise during the last two periods of observation. The clearances remained low while the blood urea nitrogen was rising, and did not rise until after it had begun to fall. On the higher diet, there was an immediate and progressive rise for a period of 6 hours. During all this time, the blood urea nitrogen was rising. These increases in clearances may probably be attributed to the specific dynamic action of the protein and the accompanying increase in metabolic rate and cardiac output, so that the increase is similar to that found in hyperthyroidism rather than to the change

TABLE 3.—THE EFFECT OF MEALS ON THE MAXIMUM UREA CLEARANCE.

Subject B, height 171 cm., weight 65.4 kg., 200 cc. H_2O per hour.

40 gm. diet fasting.				40 gm. diet with meals; 13 gm. protein at 8 A.M., 12, 5 P.M.			
Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clearance, cc./min.	Time.	Urine vol., cc./min.	Blood urea N, mg./100 cc.	Clearance, cc./min.
7:29				7:31			
8:28	6.61	7.9	66.7	8:30	3.60	7.2	62.1
9:20	1.90	7.8	*67.9	9:28	8.72	7.2	78.4
9:51	5.36	7.7	61.7	10:25	9.36	7.2	78.1
10:26	8.92	7.6	67.2	11:30	5.57	7.2	68.0
11:11	5.16	7.5	62.0	12:30	2.47	7.2	67.3
11:54	4.33	7.4	67.3	1:30	5.90	7.2	71.6
12:30	3.78	7.3	68.5	2:26	6.23	7.2	72.3
1:10	4.60	7.2	64.5	3:30	3.56	7.2	62.7
1:40	8.77	7.1	67.9	4:28	6.98	7.2	67.4
				5:21	3.13	7.3	57.0
				6:27	1.88	7.3	*48.0
				7:29	4.52	7.3	106.6
				8:30	4.51	7.3	64.6
Mean:		65.82 σ = 2.62				71.30 σ = 12.73	

* Standard clearance, not included in averages.

100 gm. diet fasting.				100 gm. diet with meals; 30 gm. protein at 8 A.M., 30 at 11:45 A.M., 40 at 5 P.M.			
8:30				7:30			
9:01	9.02	10.1	72.8	8:32	6.34	9.6	78.6
9:30	10.57	10.1	64.8	9:27	7.78	9.9	81.4
10:01	7.39	10.1	61.2	10:30	3.49	10.1	81.3
10:30	7.83	10.1	69.0	11:33	4.13	10.4	77.1
11:00	6.80	9.9	61.3	12:48	1.43	10.5	*63.2
11:30	6.14	9.8	52.5	1:30	6.62	10.5	82.0
12:00	5.67	9.6	58.3	2:30	2.30	10.6	82.7
12:30	4.67	9.5	54.0	3:15	3.02	10.6	80.3
1:00	4.77	9.3	76.7	4:00	4.22	11.2	82.8
				4:45	2.47	11.8	68.4
				5:30	3.02	12.5	81.8
				6:15	3.38	13.1	69.2
				7:00	3.07	13.7	81.0
Mean:		63.28 σ = 8.209				78.73 σ = 4.998	

* Standard clearance, not included in averages.

Subject L., height 163 cm., weight 64 kg., 300 cc. H_2O per hour.

75 gm. diet fasting.				75 gm. diet with meals; 20 gm. protein at 8:20 A.M., 22 at 12, 33 at 5 P.M.			
8:10				6:55			
8:42	5.28	9.5	59.4	7:27	8.04	11.6	69.6
9:09	7.59	9.5	69.0	7:53	9.31	11.6	66.9
9:36	7.64	9.5	62.5	8:20	lost		
10:06	6.87	9.5	63.0	8:46	9.34	11.6	73.6
10:35	7.86	9.5	68.0	9:15	10.17	11.6	86.0
11:00	6.40	9.5	59.7	9:45	10.66	11.6	78.9
11:30	7.30	9.5	66.0	10:15	7.40	11.6	78.2
11:58	7.86	9.5	71.4	10:45	9.50	11.6	83.8
12:28	5.80	9.5	61.7	11:15	8.23	11.6	78.2
				11:45	7.50	11.6	73.2
				12:28	7.30	11.6	72.4
				1:00	2.13	11.6	62.6
				1:30	3.17	11.6	82.0
				2:00	9.46	11.6	89.9
				2:30	9.94	11.6	86.4
				3:00	8.14	11.6	78.8
Average:		64.52 σ = 4.29				77.36 σ = 6.91	

in basal clearances found on low and high diets. The lag in clearance increase on the low protein diet is more consistent with Lusk's[8] finding that after a low protein diet the specific dynamic action of proteins is disturbed, than with the findings of Strang and McClugage[17] that the specific dynamic action is unaffected as long as the subject is in nitrogen equilibrium. This subject was in nitrogen equilibrium on both occasions.

TABLE 4.—EFFECT OF A SINGLE HIGH PROTEIN MEAL UPON CLEARANCES IN SUBJECT L.

Previous diet = 19 gm. From 9:30–10:00 (meal containing 114 gm. protein).				Previous diet = 120 gm. From 9:00–10:00 (meal containing 108 gm. protein).			
Time.	Urine vol., cc./min.	B.U.N., mg./100 cc.	Clearance, cc.	Time.	Urine vol., cc./min.	B.U.N., mg./100 cc.	Clearance, cc.
8:00– 8:34	8.51	5.38	63.1	7:00– 8:00	8.21	12.14	60.3
8:30– 9:04	9.08	5.35	68.4	8:00– 9:00	11.58	12.28	79.9
9:00– 9:33	10.71	5.32	55.2	9:00–10:00	4.68	12.22	72.2
9:30–10:30	3.98	6.08	55.5	10:00–11:00	3.15	12.53	78.2
10:30–11:30	4.60	7.17	72.1	11:00–12:00	3.48	13.79	88.7
11:30–12:30	4.10	12.16	51.0	12:00– 1:00	5.38	14.92	90.1
12:30– 1:30	3.92	17.14	42.2	1:00– 2:00	4.55	16.58	95.8
1:30– 2:30	4.26	18.34	54.6	2:00– 3:00	9.54	17.95	102.8
2:30– 3:30	7.03	19.54	46.5	3:00– 4:00	9.25	18.75	99.6
3:30– 4:30	5.70	16.09	68.3	4:00– 5:00	8.82	19.20	103.1
4:30– 5:30	10.17	12.64	100.0	5:00– 6:00	11.74	19.39	102.8

Summary. In a normal subject in nitrogen equilibrium there is a progressive increase in maximum urea clearance when dietary protein is increased from 0.3 to 2.4 gm. per kilo but no further increase in clearance with greater protein intake. This was not accompanied by detectable change in basal metabolic rate or cardiac output. The urea/inulin clearance ratio was not changed.

Fasting blood urea nitrogen also increases progressively with the dietary protein up to about the same level of protein intake, and is not further increased by higher protein diets.

The increased clearance on high protein diet is not due to the elevated blood urea nitrogen. It is suggested that it may be brought about by increased renal blood flow due to intrarenal vascular adjustments mediated through the higher concentration of amino-acids on high protein diets.

Progressive increase in blood urea nitrogen on high protein diets is apparently prevented by increased urine output, giving maximum clearances for a greater part of the 24 hours.

The effect of meals on maximum urea clearance varies with the amount of protein ingested and with the previous level of nitrogen intake. While the mean clearance on a day when meals are eaten is higher than when fasting, the variability is just as great and the difference not sufficient to require that clearances be determined fasting for routine work.

For the greatest precision, however, maximum urea clearances should be determined with the subject fasting, and cognizance taken of the previous diet. Since, however, there is little change in clearance with diets of 40 gm. protein and above, if the fasting

blood urea nitrogen is above 6 mg. per 100 cc. it can be assumed that the previous diet has contained enough protein to give maximum clearances.

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BRONCHOPNEUMONIA OF UNKNOWN ETIOLOGY IN A GIRLS' SCHOOL.*

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During a 6 weeks' period from November 25, 1940, to January 7, 1941, 13 cases of pneumonia occurred in a girls' school in northern Virginia. The school consists of approximately 90 girls, giving a case incidence of 14.4%.

Epidemiology. The school is situated at some distance from any town with but little contact with people from the outside. However, on November 14 the entire student body went to a church fair in a nearby village; and on November 20, Thanksgiving Day, a general homecoming for alumnæ and friends was held at the school. At this time more than 500 people came to the school and in the afternoon groups of 12 to 15 girls visited various houses in the neighborhood. The girls range from 13 to 18 years of age. They live in four separate houses according to their class in school. The fourth year students live and eat in a house of their own, ¼ mile from the main school. In this group, no person was affected. In addition to the student body, there are about 80 members of the faculty and service force, none of whom contracted the disease. The local physicians in this area met with no similar cases in their practices outside the school. The girls in the three lower classes eat in a

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common dining room but there are no permanent seating arrangements. In study hall and assembly girls of all four classes come together. All the students sleep on sleeping porches, 2 to 7 on a porch. On one porch with 7 girls, 4 of them contracted the disease. There is only 1 instance of room-mates affected. Four cases occurred in girls using the same bathrooms. The cases developed in the following sequence: November 25, 2 cases; November 27, 1 case; November 29, 1 case; December 2, 2 cases; thereafter 1 case on December 4, 8, 9, 12, 18, 21, and January 7. None of the physicians or nurses attending these patients developed the disease. The grandmother of Case 7, who visited the patient in the hospital, developed pneumonia 11 days later. She was said to have pneumococcus Type XIV lobar pneumonia with leukocytosis and recovered rapidly after treatment with sulfathiazol, begun on the fifth day of this illness. The room-mate of Case 11 developed pneumonia in Colorado Springs during the Christmas holidays. Her physician has answered none of my letters of inquiry. The school understood that the physician called this a pneumococcus pneumonia. We can draw no definite conclusions about the incubation period. However, the sequence in which new cases developed suggested that it might range between 7 and 22 days. In the first year house cases occurred on the 19th, 20th and 22d days after Case 1 became ill. Case 12 became ill 20 days after leaving school for Christmas. While at home she had no contact with any person from the school. In the other two houses cases developed from 2 to 19 days after the original case occurred. Kneeland and Smetana[9] thought that the incubation period of their cases was between 2 and 3 weeks. Longcope's[10] cases seem to indicate a similar period of incubation. It seems apparent that this outbreak was due to person to person contact.

Clinical Picture. The onset in this group of cases was, as a rule, abrupt. Headache was the presenting symptom in 10 of the 13 cases. Sore throat was complained of in 11 instances, but within 48 hours after onset this symptom cleared. Shortly after onset in all instances a characteristic, harsh, non-productive cough developed which was frequently paroxysmal. Change in position and examination of the chest produced paroxysms of coughing. Three patients complained of chilliness and 1 had an actual shaking chill. Substernal tightness and chest soreness were present in a few cases but actual chest pain was conspicuously absent. Fever occurred early in most cases, mounting to its maximum level of 100° F. to 105° F. after a few days. It was swinging in type, generally highest in the afternoon. In 1 case fever above 99° F. was present for only 1 day. The longest febrile period was 14 days, average about 8 days. The illness in these girls was definitely mild, except in 1 case where significant cyanosis and signs of toxicity occurred. This case, in its severity, would fall into Group II of Longcope's classification.[10]

There was a complete absence of influenza-like symptoms preceding and during the disease.

At the onset, physical examination revealed no abnormality in the majority of instances, though occasionally there was a slight injection of the pharynx. The pulse and respiration were, as a rule, only slightly elevated. Abnormal signs in the chest appeared anywhere from the third to the tenth day of the illness. At first these consisted of a few localized subcrepitant râles, most frequently heard in one or the other interscapular region without change of percussion note or breath sounds. Gradually impairment of percussion note developed, associated with suppression of breath sounds and an increase in large moist râles. The signs in the majority of instances slowly involved the major part of the affected lobe, though some cases showed no increase in the original signs. In only 3 patients did bronchial breathing develop. Restriction of movement of the involved chest on inspiration was striking in 3 individuals whose other lung signs were minimal. As the disease terminated, diffuse moisture often developed over the entire lobe and in several instances râles were numerous over the entire affected side of the chest. Clearing of physical signs, particularly dullness, was rapid, though a few râles were still audible in all cases on discharge.

Laboratory Findings. Blood cultures were done in 7 cases and none showed any growth. Lack of sputum was striking and made examination possible in only 4 cases. Pneumococcus Type XIX was found in 1 case and Type VI in another. However, *Micro. catarrhalis* and *Staph. albus* and *aureus* and *Strep. viridans* were the predominant organisms. *Blood picture:* All cases showed leukopenia or normal counts. The differential counts were normal except in 2 instances in which there was a moderate lymphocytosis. The leukocyte count was done at frequent intervals but leukocytosis did not occur toward the termination of the disease as reported by Longcope[10] and Murray.[13]

Roentgen Ray Examination. Roentgen ray films made early in the disease may show only slight infiltration in the region of the hilus associated with accentuation of the bronchial markings extending into one of the lobes. Gradually a definite soft infiltration of the lung parenchyma develops. This as a rule does not involve the entire lobe nor does it develop the density ordinarily seen in true lobar pneumonia. Sometimes this infiltration involves a wedge leading to the periphery. In 4 of our cases Roentgen ray films showed a spread to another lobe prior to the development of physical signs. This spread was usually not accompanied by increase in severity of the illness. Clearing of the infiltration took place rapidly after the disappearance of fever so that little or no residual shadow was left in the film.

Complications. During convalescence 1 patient developed nausea and vomiting with pain in the right lower quadrant simulating

acute appendicitis but disappearing in 36 hours. No nervous system symptoms as described by Reimann[14] occurred in this group.

Treatment. Four cases were treated with sulfathiazol without beneficial effect, so the drug was discontinued. In the other cases treatment was purely symptomatic.

Prognosis. Convalescence in this group was extremely rapid. There were no deaths.

Case Reports. Table 1 summarizes the significant findings in the 13 cases. None of these patients had heart disease or any other chronic illness. The past histories in all these young girls was of no importance in their illness. None had suffered with any disease aside from the simpler illnesses of childhood. Case 1 is reported in detail to give a clear picture of the disease; the other cases are reported in brief.

TABLE 1.

Case No.	Date of onset.	Fever.			Lung involvement.	Leukocytes.	Polys., %.	Blood culture.	Animal inoculation.	Sputum.
		Maximum.	Character.	Duration, days.						
1	11-29-40	103°	Swinging	14	L.U.L.: L.L.L.	7,100	67	No growth	Negative	*Micro. Catarrhalis; Staph. albus;* pneumococcus Type VI.
2	11-22-40	102°	Swinging	12	R.L.L.	6,000	60	Not made	Not done	None obtainable.
3	11-25-40	104°	Swinging	8	R.L.L.	6,600	64	No growth	Not done	*Micro. catarrhalis; Staph. albus*
4	11-25-40	103°	Swinging	7	L.L.L.	Not done		Not done	Not done	Not examined.
5	12- 2-40	100°	Swinging	14	R.L.L.	Not done		Not done	Not done	Not examined.
6	12- 2-40	102°	Swinging	15	L.L.L.	11,000	80	No growth	Negative	None obtainable.
7	12- 4-40	102°	Swinging	13	L.L.L.	10,000	62	No growth	Negative	None obtainable.
8	12- 8-40	105°	Swinging	8	R.L.L.	6,400	70	No growth	Negative	Not obtainable.
9	12- 5-40	101°	Swinging	9	L.U.L.: R.M.L.	8,500	72	No growth	Negative	None obtainable.
10	12-12-40	99°	Flat	1	R.M.L.	5,100	55	Not made	Negative	*Micro. catarrhalis; Strep. hemolyticus;* pneumoc. Type XIX.
11	12-18-40	102°	Swinging	7	R.L.L.: L.L.L.	5,500	60	Not made	Not done	None obtainable.
12	1- 7-41	102.5°	Swinging	14	R.L.L.	10,000	75	Not made	Not done	*Staph. albus; Strep. hemolyticus; Micro. catarrhalis.*
13	12-21-40	101°	Swinging	14	L.L.L.	Not done		Not made	Not done	Not examined.

CASE 1.—M. L. S., aged 14, became ill with headache, nasal congestion and sore throat associated with fever of 100°. The following day an unproductive cough developed but the sore throat cleared. While in the school infirmary, she ran a swinging temperature ranging from 99° to 103° (Fig. 1). On admission to the hospital on the eighth day of the illness her temperature was 101°, pulse 120, respirations 36. The patient appeared acutely ill and coughed persistently in a queer dry, metallic way. Any change of position initiated cough and chest examination produced marked paroxysms. There was moderate cyanosis of the lips and nail beds. There was a striking lag of the left upper chest on inspiration associated with moderate dullness and numerous moist, bubbling râles in this region. There was slight nasal congestion. No sputum could be obtained for

typing. A Roentgen ray film on the eighth day showed "an area of infiltration on the left side between the level of the second and fourth ribs anteriorly" (Fig. 2). Sulfathiazol was given in dosage adequate to produce a blood level of 5 mg. per 100 cc. On the eighth day of the illness, pneumococcus Type VI was obtained from a mouse which had been injected

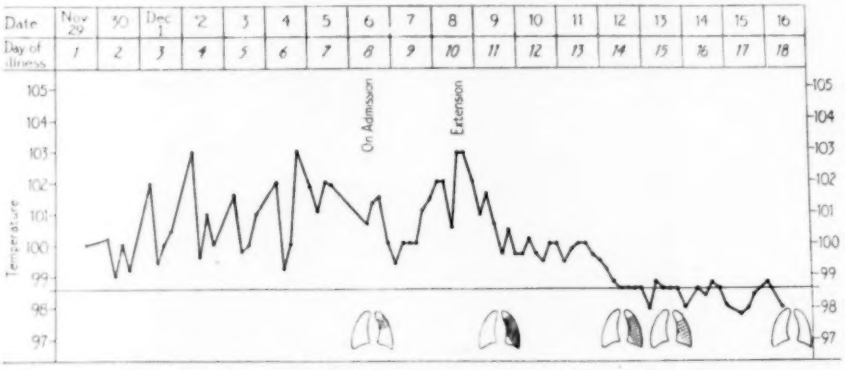

FIG. 1.—Case 1. Graphic record of temperature and lung findings.

with sputum intraperitoneally. Culture also showed *Micro. catarrhalis* and *Staph. albus*. On the tenth day of the illness the patient was definitely worse and the temperature rose to 103°. At this time impairment of percussion with scattered subcrepitant râles was noted over the left lower lobe posteriorly and distant bronchial breathing had developed over the left upper lobe. A Roentgen ray film showed an extension of the infiltration

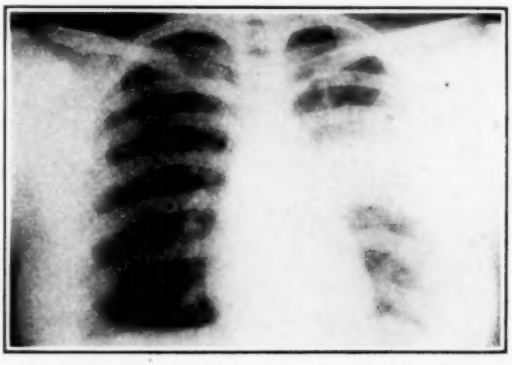

FIG. 2.—Case 1. Roentgen ray film of chest on eighth day of illness.

in the left upper lobe and the development of an inflammatory process in the left lower lobe (Fig. 3). After 3 days of sulfathiazol, the drug was stopped because it had been ineffectual and because on this day 2 other students from the school came under my care with the same illness. This made me feel that "Pneumonia-X" was the cause of the patient's illness. Improvement gradually occurred and the temperature reached normal on the fourteenth day of the illness. At this time pneumococcus Type VI was again cultured from the sputum. Roentgen ray examination on the

eighteenth day showed practically complete clearing (Fig. 4). Moist râles were still present over the entire left chest. There were, too, numerous sibilant and sonorous râles over the right chest. Convalescence was uneventful.

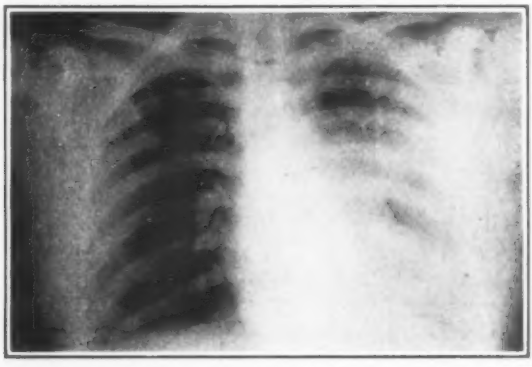

FIG. 3.—Case 1. Roentgen ray film of chest on tenth day of illness.

CASE 2.—(Courtesy of Dr. Montgomery Blair.) M. M., aged 15, developed headache, sore throat and fever shortly followed by persistent dry cough, often paroxysmal. On the tenth day râles were heard at both bases and a Roentgen ray showed a fairly extensive pneumonic infiltration involving the right lower lobe, with mild peribronchial infiltration on the

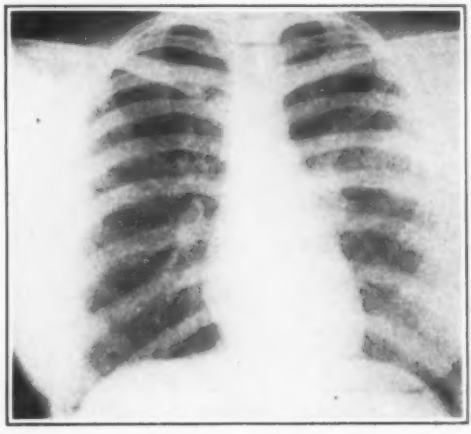

FIG. 4.—Case 1. Roentgen ray film of chest on eighteenth day of illness.

left (Fig. 5). Her illness was mild and by the seventeenth day the chest examination and Roentgen ray films showed no abnormality.

CASE 3.—(Courtesy of Dr. John Minor.) H. S., aged 17, became suddenly ill with headache, chilliness and fever. Dry cough developed on the second day. On the fourth day slight dullness and bronchial breathing were found over the right base posteriorly and later numerous moist râles were heard. Roentgen ray showed a diffuse opacity over the right lower

lobe (Fig. 6), but by the fourteenth day very little infiltration was noted in the film. This patient was the room-mate of Case 6 and slept on the porch with Cases 6, 9 and 10. She used the same bathroom with Cases 6 and 10.

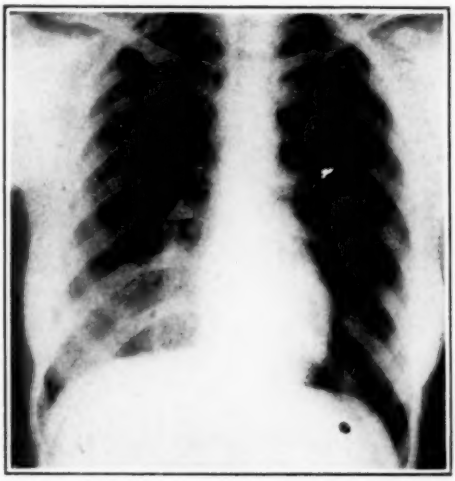

FIG. 5.—Case 2. Roentgen ray film of chest on tenth day of illness.

CASE 4.—(Courtesy of Dr. Homer A. Spitler.) W. M., aged 16, developed headache with mild fever, and on the following day, sore throat and dry, metallic cough. Late in the disease moist râles were noted over one base posteriorly. No Roentgen ray was made. Her illness was mild so that she was not admitted to the hospital.

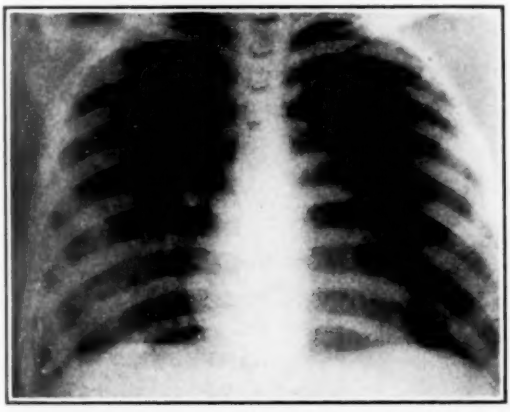

FIG. 6.—Case 3. Roentgen ray film of chest on fourth day of illness.

CASE 5.—C. D., aged 16, began with headache, malaise and cough. Persistent dry, metallic cough with very mild fever continued. When first seen on the eleventh day of the disease there was dullness, distant breath sounds and moist râles at the right base posteriorly. During con-

valescence she developed right lower quadrant pain and tenderness with nausea and vomiting. This cleared in 36 hours. Roentgen ray at this time showed mild peribronchial infiltration on both sides.

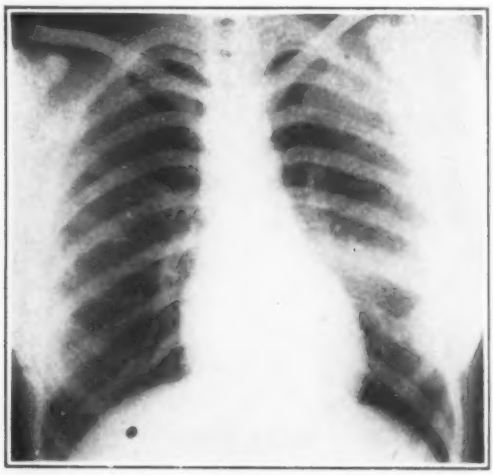

FIG. 7.—Case 6. Roentgen ray film of chest on fifth day of illness.

CASE 6.—V. J., aged 16, became suddenly ill with headache, malaise, sore throat, cough and fever. Her cough was persistent, dry and metallic. On the fifth day limitation of motion, dullness and moist râles developed over the left lower lobe. Roentgen ray films showed a slight infiltration in the mid-portion of the left chest (Fig. 7). This had completely cleared

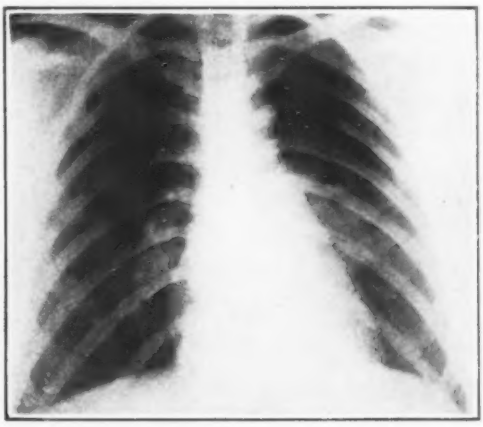

FIG. 8. Case 7. Roentgen ray film of chest on seventh day of illness.

in films taken on the twelfth day of the illness. This patient was the room-mate of Case 3, slept on the porch with Cases 3, 9, and 10, and used the same bathroom with Cases 3 and 10. Her grandmother developed

pneumonia 11 days after visiting her in the hospital. This was said to be due to pneumococcus Type XIV.

CASE 7.—C. H., aged 17, started with sore throat, headache, cough and fever. The dry cough persisted. On the fourth day there were no chest signs but the Roentgen ray showed a small area of infiltration extending out from the right hilum. By the eighth day râles had developed in the

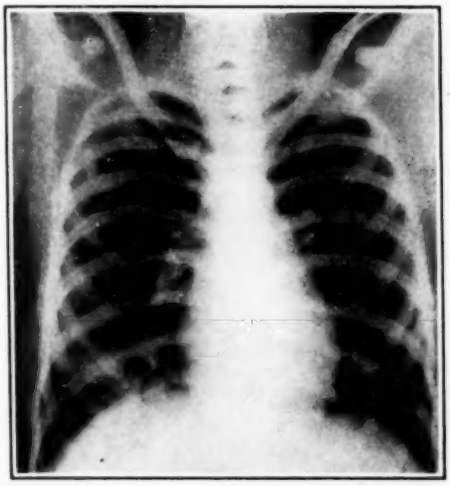

FIG. 9.—Case 8. Roentgen ray film of chest on third day of illness.

left interscapular region and a film showed a moderate infiltration throughout the lower half of the left lung (Fig. 8). Later impairment, suppression of breath sounds and râles developed in this area. On the sixteenth day the Roentgen ray showed almost complete clearing.

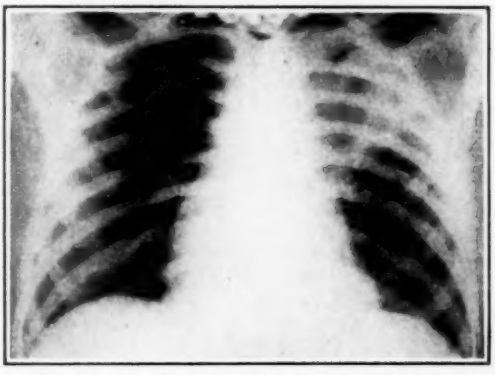

FIG. 10.—Case 9. Roentgen ray film of chest on fifth day of illness.

CASE 8.—E. A., aged 15, developed headache, malaise and sore throat followed by dry, non-productive cough. Her temperature was high but she was only mildly ill. On the third day impairment of percussion and

râles developed at the extreme right base, gradually spreading over the entire lobe. The film showed a soft infiltration throughout this area (Fig. 9) but by the tenth day this had largely cleared.

CASE 9.—M. C., aged 17, became ill insidiously with malaise and sore throat. On the third day, dry, non-productive cough and fever had developed. By the fifth day there was a marked lag of the left upper chest on inspiration associated with faint impairment but no râles. Later bronchial breathing developed in this area and the pneumonia spread to the right lung as indicated by râles in the right interscapular region. A film on the eleventh day showed a rather dense infiltration in the left upper lobe with faint infiltration in the right lower lobe (Fig. 10). This patient slept on the porch with Cases 3, 6 and 10.

CASE 10.—E. V., aged 15, gradually developed hoarseness and dry cough without fever. On the third day fever of 101° occurred but thereafter never rose above 99°. There were no chest signs until the fourth day when a few râles developed in the right interscapular region. At this time a Roentgen ray film showed a slight infiltration in the mid-portion of the right chest (Fig. 11). On the ninth day this had cleared markedly, but sibilant râles were still heard over the entire right chest.

FIG. 11.—Case 10. Roentgen ray film of chest on fourth day of illness.

CASE 11.—(Courtesy of Dr. John Diven.) A. H., aged 14, developed fever with no other symptoms on arriving home for the Christmas holidays. She later developed a dry non-productive cough with impairment over the left and then the right lower lobes, associated with suppressed breath sounds and a few scattered râles. A Roentgen ray film on the fifth day showed an infiltration involving portions of both lower lobes (Fig. 12). By the thirteenth day this had almost cleared. Her room-mate developed pneumonia of unknown character while away from the school at Christmas.

CASE 12.—J. B., aged 14, developed coryza, hoarseness, cough and slight fever on the day she returned to school after the Christmas holidays. Twenty days had elapsed since she had been in contact with any girl from the school. Her cough was mildly productive and there was nausea, vomiting and insomnia. On the tenth day râles developed in the right inter-

scapular region with the gradual development of moderate dullness, suppression and râles over the right lower lobe. Roentgen ray on the seventh day showed mild peribronchial infiltration extending into the right lower lobe, and by the ninth day, there was slight but definite infiltration there.

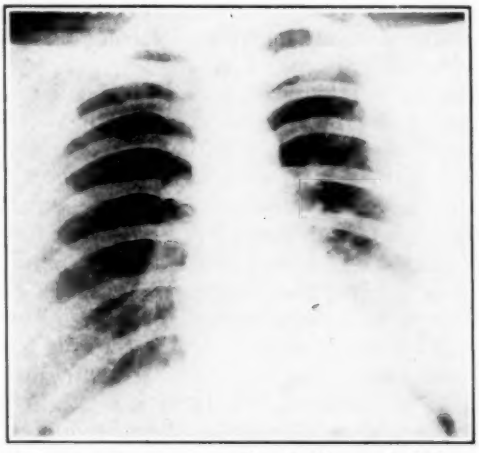

FIG. 12.—Case 11. Roentgen ray film of chest on sixth day of illness.

CASE 13.—(Courtesy of Dr. Walter F. Davey.) J. C., aged 15, had a gradual onset with malaise, general aching and fever while away from school for the Christmas holidays. Persistent dry, hacking cough began and later became productive of mucopurulent sputum. Late in the disease a few râles became audible at the bases.

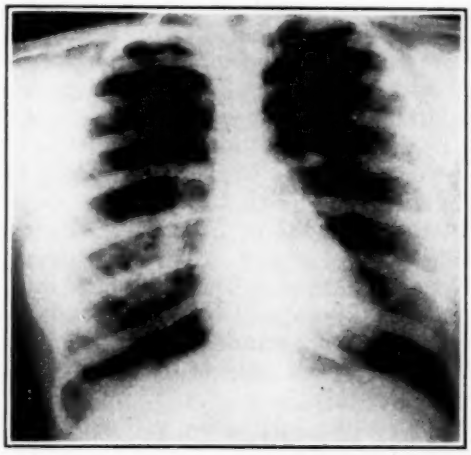

FIG. 13.—Case 12. Roentgen ray film of chest on ninth day of illness.

Discussion. This group of cases is strikingly similar to those reported by Bowen,[3] Gallagher,[7] Allen,[1] and others.[8,11,12,16,17] The

case incidence in a brief period is greater in this outbreak than in any we have seen previously reported. This epidemic differs from that described by Reimann and Havens[15] and others in that the patients did not show evidence of a grippe-like infection prior to the onset of lung involvement. During the period when these cases occurred the school was notably free of common colds and other upper respiratory infections.

The diagnosis of isolated cases of this disease may be extremely difficult when there is no epidemic. It might be well to repeat here the features that differentiate this entity from true lobar pneumonia. 1, The onset is usually mild without chill or chest pain. 2, The cough is dry, metallic, non-productive and often paroxysmal. It is so characteristic that after hearing it in the first few patients one could almost make a diagnosis in the later cases from the nature of the cough. 3, If sputum can be obtained it is not rusty and does not consistently contain pneumococci. 4, Leukocytosis with polymorphonuclear increase is absent. 5, Herpes does not occur. 6, The illness is usually mild and not accompanied by toxemia. 7, The fever is swinging in character. 8, There is a paucity of chest findings and rarely evidence of complete lobar solidification. 9, The areas of infiltration shown in the roentgenograms are less dense and do not as a rule involve the entire lobe. The films, however, show more involvement than physical examination would lead one to expect. 10, This disease is more apt to occur in mid-winter than in late winter and spring. 11, It is definitely more communicable. 12, Chemotherapeusis is of no value.

It was suggested by Bock[2] in 1938 that the great majority of these cases represented virus pneumonia. Reimann[14] obtained a filterable virus from the blood of 1 patient and from the nasopharyngeal washings of another. A lung inflammation in experimental animals was produced with this agent. However, after several passages, the virus was lost. In 1940, during an outbreak of this disease at the National Institute of Health in Washington, D. C., Dyer and Topping[6] isolated a rickettsia from the blood and nasopharyngeal washings of 3 patients. This they identified as the same rickettsia isolated by Burnett[4] in 1937 in "Q" fever. Weir and Horsfall[18] recently reported the isolation of a virus from the throat washings of cases of this type. This virus when inoculated into the mongoose produces pulmonary consolidation. It was not pathogenic for various other animals. The serum of human beings who had recovered from this disease was capable of protecting the mongoose against infection with this virus.

Dyer and Topping inoculated mice, guinea pigs and the chorioallantoic membrane of hen's eggs with blood and pharyngeal washings from 6 of our cases. No rickettsia or virus was isolated. They had the misfortune of having secondary infections in both their inoculated and control animals. For this reason we do not feel

that this is a valid negative. The materials were obtained from only 3 patients early in the disease.

Table 2 summarizes the primary inoculations from our 6 patients to various animals. In any case where a primarily inoculated animal showed any abnormality whatsoever material was taken from him and passed through serial passages into other animals including the chick embryo.

TABLE 2.—RESULTS OF ANIMAL INOCULATIONS FROM 6 CASES.

Case No.	Day of illness.	Guinea pigs. Number used, material and route of inoculation.	Mice. Number used, material and route of inoculation.	Chick embryos.
1	10th	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	
6	5th	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	
7	5th	....	2: Saline gargle: I.P. 2: Saline gargle: I.N.	
8	2d	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	Yes; blood and saline gargle.
9	2d	2: Blood: I.P.	2: Blood: I.P. 2: Saline gargle: I.N.	Yes, blood and saline gargle.
10	3d	2: Blood: I.P.	2: Blood: I.P. 2: Serum: I.C.	

A variety of names has been applied to this clinical entity: "Acute Influenza Pneumonitis" (Bowen[3]); "Type A Virus Pneumonia" (Reimann[14]); "Acute Interstitial Pneumonia" (Smiley[17]); "Focal Disseminated Pneumonia" (Scadding[16]); "Atypical Bronchopneumonia" (Murray[13]); "Atypical Pneumonia" (Cass[5]); "Broncho-Pneumonia, Variety X" (Longcope[10]). The term pneumonia has always meant inflammation in the lung regardless of etiology. There seems, therefore, no reason to speak of these cases as pneumonitis. It would seem wise at this time to follow Longcope's lead and speak of this disease as bronchopneumonia of unknown etiology, Variety X, until the causative agent is established beyond question.

Summary. An outbreak of bronchopneumonia in a girls' school occurred between November 25, 1940, and January 7, 1941, affecting 13 of 90 students, an incidence of 14.4%. Previously reported outbreaks have been largely among males. The illness began, as a rule, abruptly with headache, mild sore throat and fever. This was shortly followed by a characteristic dry, harsh, non-productive cough. Abnormal lung findings were absent early, and even later in the disease were less than would be expected in patients having definite lung infiltration. Leukopenia or normal leukocyte counts were present and the sputum contained a mixed flora. Roentgen ray films of the chest usually showed an infiltration of moderate density beginning at the hilum and later extending in a fan-like fashion towards the periphery of the lung. This was usually limited to one lobe. The disease was mild in character and rarely accompanied by toxemia. Fever persisted for from 1 to 14 days. There were

no deaths. No virus or rickettsia were obtained by animal inoculations.

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CORRELATION BETWEEN CLINICAL AND IN VITRO REACTIONS OF GONOCOCCUS STRAINS TO SULFATHIAZOLE.

(A PRELIMINARY REPORT.)

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FELKE,[1] Levaditi and Vaisman,[4] and Herrold[2] have reported the occurrence of gonococcus strains which were resistant to sulfanilamide. Westphal, Charles and Carpenter[5] developed, experimentally, strains resistant to sulfapyridine.

The following *in vitro* bactericidal test, a modification of the technique developed by Keefer and his coworkers,[3] demonstrated gonococcus strain reactions to sulfathiazole which corresponded to the results of chemotherapy in the patient.

Method. The test was carried out as follows: Citrated blood obtained from patients who had received 2 gm. of sulfathiazole 4 hours previous to the taking of the blood was divided into two parts, one of which was inactivated at 56° C. for 30 minutes. Various saline dilutions (10^{-1}, 10^{-3}, 10^{-5}) of a 24-hour growth of gonococci in 20% ascitic broth were added in 0.1 cc. amounts to tubes containing 0.5 cc. of the active or inactivated blood. The inoculated blood was incubated for 24 hours at 36° C. and 0.1 cc. from each tube was pipetted on to cooked blood filtrate ascitic fluid agar plates. These were incubated at 36° C. for 48 hours before being read.

Controls were set up by substituting 20% ascitic broth for the blood, and adding 4 mg. per 100 cc. of sulfathiazole.

Experiments were also made by adding p-aminobenzoic acid[6] to the tubes containing sulfathiazole in blood or ascitic broth so that the final concentration of the acid was 5 mg. per 100 cc.

Active blood containing sulfathiazole did not give evidence of gonococcus strain differences. However, such differences of behavior were clearly demonstrated when inactivated blood was used. It was found that most strains obtained from patients who had responded to sulfathiazole did not grow in inactivated blood containing the drug, even with the higher concentrations of the organisms. On the other hand, strains obtained from patients who did not respond to therapy often showed growth with dilutions of 10^{-5} of the organisms (Table 1). This strain difference was not so evident when ascitic broth was used instead of inactivated blood.

TABLE 1.—EFFECT OF INACTIVATED HUMAN BLOOD CONTAINING SULFATHIAZOLE ON THE VIABILITY OF GONOCOCCUS STRAINS.

Dilutions of broth culture of gonococci:		10^{-1}		10^{-3}		10^{-5}	
Strain.	No. of tests.	+	O.	+	O.	+	O.
A. Strain Susceptible to Sulfathiazole.							
S1	37	15	22	1	36	1	36
S2	22	5	17	0	22	0	22
S3	12	4	8	0	12	0	12
S4	8	0	8	0	8	0	8
S5	6	6	0	1	5	0	6
S6	5	0	5	0	5	0	5
S7	4	0	4	0	4	0	4
S8	3	0	3	0	3	0	3
S18*	2	2	0	0	2	0	2
B. Strains Resistant to Sulfathiazole.							
R1	56	56	0	55	1	44	12
R3	11	11	0	9	2	6	5
R4	11	10	1	9	2	7	4
R5	9	9	0	8	1	5	4
R6	7	7	0	7	0	2	5
R7	5	5	0	5	0	2	3
R8	5	5	0	3	2	1	4

+ = Growth. O = No growth.

* With 8 other susceptible strains, one test for each showed no growth in all 3 dilutions.

Comparison of the bactericidal power of blood containing sulfathiazole with the same blood containing p-aminobenzoic acid in addition, showed that susceptible strains were protected from the action of the sulfathiazole by the acid while resistant strains were either unaffected or made more susceptible to the action of the drug (Table 2).

Two strains, S7 and S8, obtained from patients who were apparently carriers, acted like susceptible strains. Each time the patients were given sulfathiazole, they appeared to respond in the typical manner, only to show a recurrence at a later date.

It was found that the behavior of a particular strain of organisms once isolated from the host, remained unchanged, in spite of the numerous passages on artificial media. However, it is known that some patients do not respond to the first course of treatment, but may respond to a second or third course. This makes one suspect

the existence of a host factor which was not demonstrated by the test.

TABLE 2.—EFFECT OF INACTIVATED HUMAN BLOOD CONTAINING SULFATHIAZOLE AND P-AMINO BENZOIC ACID ON THE VIABILITY OF GONOCOCCUS STRAINS.

Dilutions of broth culture of gonococci:		10^{-1}		10^{-2}		10^{-3}	
Strain.	No. of tests.	+	O.	+	O.	+	O.
A. Susceptibe Strains.							
S1	6	6	O	6	O	5	1
S2	3	3	O	3	O	2	1
S6	5	5	O	5	O	5	O
B. Resistant Strains.							
R1	10	10	O	7	3	3	7
R4	9	9	O	8	1	6	3
R5	9	9	O	9	O	8	1
R6	1	1	O	1	O	1	O
R7	5	5	O	5	O	3	2

+ = Growth. O = No growth.

There was a lack of clinical and laboratory correlation for 2 strains of the 34 studied. One was a susceptible strain (S18), obtained from a patient resistant to sulfathiazole therapy. The other was a resistant strain (R5), obtained from a patient who responded to sulfathiazole treatment. It is suggested that the strain may undergo a change in the host from a resistant to a responsive character. Investigation along these lines will be continued.

Summary. A technique is described which gives evidence of a difference in behavior of various gonococcus strains to sulfathiazole *in vitro*. The strain variation corresponds markedly with the clinical reaction of the patient. Para-aminobenzoic acid inhibits the bactericidal effect of sulfathiazole on susceptible strains of gonococci.

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THE FORMOL-GEL TEST IN RHEUMATIC FEVER.

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SINCE the formol-gel test was first described by Gaté and Papacostas[5] in 1920, it has been recommended as a diagnostic aid in many diseases. The reaction was thought to occur only in the

serum of syphilitic patients but it has since been found to be present in a great variety of unrelated conditions.[6,10,12]

Our attention was first drawn to the test by the report of Schultz and Rose[9] in 1939. These authors compared the formol-gel test with the erythrocyte sedimentation rate (ESR) in cases of rheumatic fever and rheumatic heart disease as well as in an assorted group of "control" cases. They found that in patients with various febrile diseases excluding rheumatic fever there was a parallelism between the ESR and the formol-gel test and that a positive formol-gel test never occurred unless a certain degree of increased erythrocyte sedimentation existed. However, in children or adults with rheumatic carditis the test became positive when signs of active carditis appeared and the results were not necessarily parallel to the ESR.

They also noted occasional instances in which the formol-gel test remained positive after the ESR had returned to normal and suggested that this test might be a more sensitive index of persisting rheumatic infection. In cases of active rheumatic carditis with decompensation the formol-gel test was positive, whereas the ESR was within normal limits. These observations suggested to the authors that the formol-gel test might be a valuable additional aid in determining the presence of active carditis in patients known to be suffering from rheumatic fever.

Material and Methods. Three hundred and thirty-eight tests were performed on 208 patients. For the most part these patients were adolescents and adults, but a few children were included. The series consisted of a large number of patients with rheumatic valvular disease of varying degrees of activity. As controls, healthy individuals and patients with a variety of diseases seen on a general hospital ward service were included.

All bloods were taken by venipuncture, placed immediately in clean test tubes and allowed to stand until clot retraction had taken place. These were not necessarily fasting specimens. The tubes were then centrifuged and 1 cc. of serum was withdrawn and placed in a small test tube of 0.8 mm. bore. Two drops of a 40% formaldehyde solution were added to each tube. The tubes were than tightly stoppered and inverted until through mixing had occurred. The tubes were inspected at intervals of 24, 48 and 72 hours and the degree of gelation recorded. Early in the work the tubes were inspected at the end of 5-minute and 1-hour intervals, but this was soon discarded, since no additional information was gained. The degree of opacity was likewise found to be of little value and was abandoned.

The following criteria were adopted to denote the degree of gelation: 1. On inversion of the tube the serum showed a slight increase in viscosity when compared with normal serum. 2. On inversion of the tube the serum flowed very slowly when compared to normal. 3. On inversion of the tube there was no flow of serum but the surface had a jelly-like consistency. 4. On inversion of the tube a solid gel was present with no movement of the surface.

The ESR determinations were done by the Westergren method as modified by Berg.[1] For the purpose of this study all rates below 20 mm. per hour were considered to be normal or borderline, while all rates over 20 mm. per hour were considered definitely abnormal.

Results. Table 1 lists our results and indicates the relation of the ESR to the formol-gel test.

In 58 patients with clinically inactive rheumatic valvular disease of various degrees and with an ESR below 20 mm. per hour, the formol-gel test was invariably negative. In 9 additional cases where the ESR was between 20 mm. and 65 mm. per hour and in whom activity may have been present without clinical manifestations, the formol-gel test was negative in 7 and slightly positive in 2 cases.

TABLE 1.

Disease.	Total No. of cases.	ESR in mm. per hour.					Formol-Gel test.*			
		0–19.	20–39.	40–59.	60–79.	80+.	Neg.	Sl.*	Mod.*	Mark.*
Normals	59	59					59			
Rheumatic fever:										
Quiescent	58	58					58			
Questionable	9		7	1	1		7	2		
Active	16		1	4	4	7	3	1	3	9
Subacute bacterial endocarditis	6				1	5	3	1		2
Coronary thrombosis	6	3	2	1			6			
Cirrhosis of liver	4		2			2		1		3
Rheumatoid arthritis	14	1	5	3	2	3	7	2	2	3
Malignancy	5	2				3	5			
Miscellaneous:										
Acute and chronic infections	31	8	6	5	5	7	26	3	1	1
Totals	208	131	23	14	13	27	174	10	6	18

* Markedly positive tests include all those with 4+ gelation after 24 hours; moderately positive tests include those with 3+ gelation in 24 hours and 3+ and 4+ gelation in 72 hours; slightly positive tests include all those of less degree than 3+ gelation at the end of 72 hours.

Sixteen cases of active rheumatic fever in the hospital wards were studied during the course of the disease. Thirteen of these cases at one time or another gave a positive formol-gel reaction which in general paralleled the ESR, particularly when the ESR was high. In 1 patient, however, with an ESR of 90 mm. per hour and showing typical migratory arthritis, subcutaneous nodules and tachycardia, the formol-gel test was never positive. Another case was that of an 8-year-old boy with severe active rheumatic pericarditis and an ESR of 133 mm. per hour. The formol-gel test was negative until late in the course of the disease when the signs of active carditis had disappeared. The diagnosis of active rheumatic carditis is often extremely difficult even with the aid of modern laboratory techniques. The electrocardiogram may be of help, but interpretations must be made with caution.[8]

Six cases of coronary thrombosis were tested. The formol-gel test was invariably negative, although the ESR was above 20 mm. per hour in 3 of the cases.

Six cases of subacute bacterial endocarditis were followed over periods of many weeks. The diagnosis was definitely established in all cases and eventually all died. Two cases showed a positive formol-gel test, 3 were always negative and 1 was sometimes posi-

tive and sometimes negative. The ESR was markedly elevated in each case.

In studying liver and gall bladder disease it was found that the formol-gel test was usually positive in cases of cirrhosis, but not invariably so. One case of acute catarrhal jaundice and 2 cases of acute cholecystitis were negative.

In 14 cases of rheumatoid arthritis the ESR was over 20 mm. per hour in each case. Seven of the cases showed a formol-gel test positive in some degree and 7 were negative. One case of gout with an ESR of 103 mm. per hour was negative.

Weltmann[11] tests were performed with the ESR and the formol-gel test in 8 selected cases, but no correlation was found.

Discussion. All evidence to date[3,4] points to the fact that the formol-gel test is a test for hyperglobulinemia and has no specificity in individual diseases. A recent paper by Biguria and Foster[2] proposed modifications of the test for the determination of globulin content of serum. Our results have likewise shown no specificity and we have been unable to corroborate many of Schultz and Rose's results. It is true that a positive formol-gel test rarely occurs with a normal sedimentation rate except in the presence of cardiac decompensation but on the other hand there is no correlation between a high ESR and the formol-gel test. Nor were we able to demonstrate that the formol-gel test was of value in determining the degree of carditis present. None of the cases of coronary occlusion with cardiac degenerative changes gave a positive test and 1 case of unquestionable rheumatic pancarditis gave negative results.

Schultz and Rose suggested that the test might be a more sensitive index of persisting rheumatic activity than the ESR. The formol-gel test may remain positive in cases of rheumatic fever after the ESR returns to normal ranges, but in our experience this alone is not an indication of persistent rheumatic activity that should keep the patient in bed. Our cases with a normal ESR but a persisting positive formol-gel test did well on gradually increasing activity, although this test often remained positive in some degree for long periods.

The formol-gel test has one advantage over the ESR in that the test does not have to be performed immediately. We have retested many sera after preserving them in the refrigerator for periods as long as 2 months and the results were essentially the same. This fact, however, does not compensate for the lack of sensitivity of the test.

Since this work was completed, a paper by Klein, Levinson and Stubik[7] has appeared covering a study of the formol-gel test, the ESR and the Weltmann reaction in the rheumatic fever of childhood. Their results were entirely similar to ours in that they were unable to substantiate the claim that the formol-gel test was a measure of rheumatic carditis. In their experience the formol-gel

test was the least sensitive of the three procedures in determining the degree of activity in patients with rheumatic fever.

Summary and Conclusions. 1. The formol-gel test is essentially a test for hyperglobulinemia and has no correlation with the erythrocyte sedimentation rate.

2. It is of little or no value in the diagnosis of acute rheumatic fever with or without carditis.

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BOOK REVIEWS AND NOTICES

DOCTORS DON'T BELIEVE IT—WHY SHOULD YOU? Facts and Fallacies About Health with Practical Guide for the Layman. By AUGUST A. THOMEN, M.D., with Introductions by LOGAN CLENDENING, M.D., and The Right Honorable LORD HORDER, Physician in Ordinary to the King of England. Pp. 384. New York: Simon and Schuster, 1941. Price, $2.50.

WRITTEN for laymen, this book will be welcomed and appreciated by all physicians because it so splendidly fulfills the promise of its subtitle. There are facts in a wide range of medical knowledge, wisely selected and well presented, interlarded with exposures of many fallacious beliefs current among the laity. The mode of presentation is ingenious and effective, taking the form of questions—254 of them—and their answers, ranging from a few words up to 30 pages. They are grouped under these chapter headings: Food, diet, and weight reduction; your daily life; major ailments; the venereal diseases; cancer; the common cold; allergy, asthma, and hay fever; minor ailments and remedies; mind and senses; birth, marriage, and death. The material is timely, accurate and interesting, so that the book should prove most popular and useful. R. K.

OUTLINES OF INDUSTRIAL MEDICAL PRACTICE. By HOWARD E. COLLIER, M.D., CH.B., Formerly Reader in Industrial Hygiene and Medicine, University of Birmingham; Certifying Factory Surgeon, etc. Pp. 440. Baltimore: The Williams & Wilkins Company, 1941. Price, $5.00.

THE problems of industrial hygiene and medicine are extensive, and a comprehensive discussion of the whole subject can hardly be presented within a single volume. The author has not attempted to do so. He has selected his material well and it is evident that it is presented from a background of considerable experience in the field of industrial medicine. While the subject is discussed from the British point of view, much of direct interest to American industrial physicians will be found. Extensive reference is made to American as well as British literature.

The subject matter is divided into five parts which are self-explanatory from their titles: Executive duties, advisory functions, industrial psychology, industrial medicine, industrial forensic medicine. The discussion of problems of industrial psychology is a welcome addition to a textbook on industrial medicine and its inclusion is indicative of the expansion of the duties of the industrial physician in the modern health program in industry. Of particular interest at the present time is the author's discussion of the influence upon the workers' efficiency and health of such factors as hours of labor, speed of work, overtime, night work, and so on. Experience during the last war showed clearly that the optimum rate of doing work could not safely be exceeded except for short periods. It is to be hoped that the mistakes of that period will not be repeated.

The discussion of industrial poisons is necessarily limited, the most important ones receiving the greatest consideration. The author would have done well to have limited it even more. A number of the less common poisons receive only brief mention. A mere listing of these substances, with suitable references, would have served as well and more space could have been given to the important toxic substances. The classification of agents causing occupational dermatoses and trade ulcers is excellent.

The final section on forensic medicine includes an excellent summary of the British laws which should serve as a basis for comparison with American practices.

The author has fulfilled in an excellent manner his purpose, which was to present an introduction to industrial medicine for those who contemplate entering this field. T. H.

THE COMPLETE WEIGHT REDUCER. By C. J. GERLING. Pp. 246. New York: Harvest House, 1941. Price, $3.00.

MUCH useful information for laymen on obesity: its causes and treatment, and especially on the many fads and quackeries that are perpetuated on the public in this field. The manner of presentation is novel. Instead of a systematic and consecutive covering of the subject, there are concise discussions, usually only a paragraph or two, on topics alphabetically arranged, to which the reader can easily refer when he wishes to look up a particular point. The book should prove helpful and instructive to the interested layman. R. K.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. Pp. 931; 431 illustrations and 2 colored plates. Fourth Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $9.50.

EACH succeeding edition of this valuable textbook brings it nearer in size to the Big Three works on this subject, without loss of quality. Favorably comparing with them is the lower price of Bell's work, and the greater attention paid to predisposing factors in disease and to physical and chemical agents. There is a welcome increase in the emphasis on pathologic physiology, and a desirable tie-up with clinical medicine, without sacrifice of space devoted to the basic concepts on general pathology.

E. K.

THE INTERVERTEBRAL DISC. With Special Reference to Rupture of the Annulus Fibrosus with Herniation of the Nucleus Pulposus. By F. KEITH BRADFORD, M.D., Houston, Texas and R. GLEN SPURLING, M.D., Louisville, Ky. Pp. 158; 45 illustrations. Springfield, Ill.; Charles C Thomas, 1941. Price, $4.00.

IN this monograph discussion of diseases and traumata of the intervertebral disc, special attention is given to the nucleus pulposus. The scope of the work is comprehensive and inclusive. Anatomy, physiology and pathology are adequately considered and clinical phases of diagnosis and treatment receive detailed study. Differential diagnosis is somewhat sketchy, and conditions producing the symptoms of herniated disc are not given a true percentage valuation.

The illustrations are excellent, the format and paper are up to the Thomas standard. This monograph is of distinct value and is a contribution worthy of study and frequent reference. G. W.

TRAUMA AND DISEASE. Edited by LEOPOLD BRAHDY, B.S., M.D., Physician in Charge of Occupational Diseases and Injuries in the Office of The Corporation Counsel of the City of New York, etc., and SAMUEL KAHN, B.S., M.D., Medical Examiner in the Bureau of Workmen's Compensation of the Department of Labor, State of New York. Pp. 655; 13 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1941. Price, $7.50.

THIS second edition continues the high standard set by the first. To the list of well-known authors who have contributed chapters have been

added Dr. Edward N. Packard, with a chapter on tuberculosis, Dr. George Blumer, who has rewritten the chapter on pulmonary diseases, and Dr. Robert J. Joplin, who has materially added to the chapter on bone diseases.

Throughout, additions have been made as knowledge has accumulated, and this is especially true in the chapter on the relation of trauma to heart disease, where recent experimental work is cited. There are a few new illustrations and, in all, about 40 new pages of text. The book remains as a very valuable possession. It should be of particular interest to physicians in compensation practice and to compensation referees and lawyers. The work differs from several other books on the same subject in that each section is written by a man who is a recognized authority in his field.

L. F.

PATHOLOGY FOR STUDENTS AND PRACTITIONERS OF DENTISTRY. By WILLIAM E. EHRICH, M.D., Associate in Pathology, School of Medicine, University of Pennsylvania. Pp. 509; 234 illustrations. Philadelphia: Lea & Febiger, 1941. Price, $5.50.

IN a short period of time several new textbooks have appeared outlining courses of pathology for dental students. Ehrich's book is not just another of these texts.

In the present educational set-up it is as a rule, deemed unnecessary to acquaint dental students with the principles of pathology as taught to medical students. If one is of this opinion then it becomes a difficult task to select from the general subject matter such material as may be suited to adequately support the study of oral disease. The author has been successful in such an attempt.

Having taught pathology to both medical and dental students he is eminently qualified to make this endeavor and we think his results testify to this fact. His correlation of systemic and local conditions is definitely aimed at widening the mental horizon of the future practitioner of dentistry, who too often regards the mouth and the teeth as anatomic entities whose rôle in the somatic functional processes is an insignificant one. We therefore welcome this effort at correlation.

Moreover, the author has integrated skillfully, where possible, the pictures of tissue changes and functional disturbances, a practice which is so essential to an understanding of disease.

The arrangement of the chapters is unusual for a textbook on pathology. Inflammation is discussed in the last chapter which places the subjects of pulpitis and parodontitis at the end of the book. Controversial topics such as parodontitis (14 pages with 13 illustrations) and caries (14 pages with 9 illustrations) might well receive more elaborate treatment in a next edition. The bibliography is definitely partial to the European literature. The literary aspect of the book could be improved upon. However, we feel that the dental student and the practitioner will be greatly benefited by reading and frequently consulting Ehrich's book. It contains much information rarely embodied in textbooks of this kind, and we therefore recommend it warmly to the dental profession.

H. C.

BODY MECHANICS IN HEALTH AND DISEASE. By JOEL E. GOLDTHWAIT, M.D., F.A.C.S., LL.D., LLOYD T. BROWN, M.D., F.A.C.S., LORING T. SWAIN, M.D., and JOHN G. KUHNS, M.D., F.A.C.S. With a Chapter on the Heart and Circulation as Related to Body Mechanics, by WILLIAM J. KERR, M.D., F.A.C.P. Pp. 316; 121 illustrations. Third Edition, completely revised and reset. Philadelphia: J. B. Lippincott Company, 1941. Price, $5.00.

THE keystone of the Boston School of Orthopædics has long been the work of Goldthwait on posture and body mechanics. In the third edition

of this work the views of Goldthwait are presented and augmented by his pupils. The greater portion of the book is sound and of value. Some wishful thinking and loose statement has, however, crept into the work. Especially is this true as regards vascular disease. Certainly the proper critical attitude has not been applied to the relationship between skeletal structure and position and the development and treatment of visceral diseases.

G. W.

IMMUNITY AGAINST ANIMAL PARASITES. By JAMES T. CULBERTSON, Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University. Pp. 274; illustrated. New York: Columbia University Press, 1941. Price, $3.50.

THE subject matter of this book is divided into three parts: 1, Natural Resistance and Acquired Immunity; 2, Immunity in Specific Diseases; and 3, Applied Immunology. Part I contains 7 chapters, the headings of which are: Natural Resistance, Age Resistance, Specifically Acquired Immunity, Requisite for Immune Response, Parasites Which Elicit Immunity, Mechanisms of Specific Immunity and Demonstration of Immunity. Part II is made up of the following 9 chapters: Amœbiases, Leishmaniases, Trypanosomiases, Malarias, Coccidioses, Trematodiases, Cestodiases, Nematodiases, and Response to Arthropods. Part III is composed of the following: Classification of Parasites, Vaccination Against Parasites, and Diagnosis of Parasitic Infection. A list of abbreviations of journal titles and an index complete the book. The text is illustrated by 4 plates, 3 charts and 2 tables.

To this Reviewer the chief value of the book is its extensive bibliography, which supplements that of Taliaferro's (1929) "The Immunology of Parasitic Infections." On the whole, one gets the impression of hurried preparation, inadequate digestion of data and of carelessness. The last may be illustrated by expressions such as "malaria-infected blood," "monkey malarias," "choice of hosts," "the balantidias" for species of balantidium, "Balantidia" written as a generic name, "somatic protozoans" for protozoa that are parasitic in tissue. Throughout the text results of experiments are cited without analytical consideration of their part in aiding a rational explanation of the interrelationships of host and parasite. There seems to have been no attempt to differentiate between truly pathogenic and nonpathogenic parasites or "normal" and "abnormal" parasitism in discussing immunologic responses. This Reviewer cannot agree that "examples of extreme maladjustment between host and parasite do not occur . . . . in natural infections" (p. 14), that "age resistance has been demonstrated to" parasitic amœbæ or flagellates of the intestinal tract (p. 37), that "once a parasite has developed to a stage which can survive in the intestinal lumen . . . . it is largely beyond the influence of the agencies . . . . which perform the immune function" (p. 60), that "the depression of egg production by female worms in immune hosts may be explained by occlusion of the genital pore with precipitate "(precipitated antibody) (p. 72), that "most human beings are naturally resistant to infection with Endamœba histolytica" (p. 92), or that eosinophile leukocytes, by collecting in the intestinal mucosa "form a definite barrier to penetration by the adult parasites" (*Trichinella spiralis*) (p. 192).

This Reviewer has no wish to belittle in any way the excellent studies that have been and are being made on the immunology of parasitic diseases. Certainly this phase of parasitology would not have attracted the attention of our best-equipped investigators had it not presented so many fascinating problems. It warrants better treatment than has been its lot this time.

H. R.

THE BAKER MEMORIAL, 1930–1939. A Study of the First Ten Years of a Unit for People of Moderate Means at the Massachusetts General Hospital. By HAVEN EMERSON, M.D. Pp. 75; 1 illustration. New York: The Commonwealth Fund, 1941.

THIS book is at once an accounting of 10 years of successful stewardship and an able appeal for other communities to develop adequate facilities for the care of our large group of citizens of moderate means.

The following paragraphs from the volume capably describe its purpose and content:

"The Baker Memorial remains unique in hospital experience with its consistent coöperative pattern, by which the supporting community, the hospital administration, the medical and nursing staffs, and the patients share in obtaining bed care of superior quality for the sick at a cost which people of moderate means can pay."

"After a brief review of the chronological development of the idea of a self-supporting hospital for private patients of moderate means, from its first expression, through the stages of discussion, acceptance, construction, and operation, the significant facts as to use of the hospital during the ten-year period will be presented and the reaction of patients and physicians considered.

"The financial experience of the hospital will be described and its economic and social implications for possible application of similar principles for hospital care in other communities will be discussed." B. B.

A BRIEF COURSE IN ORGANIC CHEMISTRY. A Combined Textbook and Laboratory Manual. By REYNOLD C. FUSON, Professor of Chemistry in the University of Illinois, RALPH CONNOR, Associate Professor of Chemistry in the University of Pennsylvania; CHARLES C. PRICE, Assistant Professor of Chemistry in the University of Illinois, and H. R. SNYDER, Assistant Professor of Chemistry in the University of Illinois. Pp. 248; 24 illustrations. New York: John Wiley & Sons, Inc., 1941. Price, $2.50.

ALTHOUGH this excellent combined textbook and laboratory manual has been designed for students of pre-medicine or related fields, it may also be of value to certain physicians who desire to have at hand a concise reference book concerned with broad, fundamental concepts in organic chemistry. The material is clearly presented, and, although condensed, is quite up-to-date. The later chapters dealing with Coal-Tar and Natural Products constitute a convenient source of information pertaining to sulfonamides, vitamins, hormones, etc. F. S.

SURGERY OF THE HEART. By E. S. J. KING, M.D., M. S., D.Sc. (Melb.), F.R.C.S. (Eng.), F.R.A.C.S., Major A.A.M.C., Honorary Surgeon to Outpatients, Royal Melbourne Hospital; Jacksonian Prizeman, Royal College of Surgeons; etc. Pp. 728; 268 illustrations and 4 color plates. Baltimore: The Williams & Wilkins Company, 1941. Price, $13.50.

THE title of this monograph is somewhat misleading. "What a Cardiac Surgeon Should Know" would more nearly describe the contents. The first third of the book is concerned with the anatomy, physiology and pathology of the heart. The second two-thirds are mainly descriptions of heart disease in the classical manner: history, etiology, pathology, symptoms and signs, treatment and prognosis of the various conditions. Only a few of the diseases of the heart are amenable to surgical therapy, but without doubt a surgeon venturing into this field should be familiar with all the conditions discussed.

The author has proved himself to be truly a doctor of medicine as well as a surgeon, and this book is to be commended as an example of the general information that the surgeon should possess rather than the purely technical information of the "operator." I. R.

HYPOPARATHYROIDISM IN DENMARK. A Clinical Study. By AAGE LACHMANN. Pp. 269; illustrated. Copenhagen: Einar Munksgaard, 1941. Price, Dan. Cr. 12.

THIS is a summary of the clinical and metabolic findings in patients with postoperative and idiopathic hypoparathyroidism, with results of various treatments. It consists of studies on patients in several Danish hospitals and analysis of data in the literature of other countries. I. Z.

THE FOOT AND ANKLE. Their Injuries, Diseases, Deformities and Disabilities with Special Application to Military Practice. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 665; 304 line drawings by HAROLD LAUFMAN, M.D. Second Edition. Philadelphia: Lea & Febiger, 1941. Price, $9.00.

THIS book is well on the way to becoming a classic. The second edition is much superior to the first. Experience has shown what to eliminate and condense. Necessity has caused inclusion and elaboration of lesions peculiar to the soldier and war. In its present form this book is of great worth and can be unhesitantly recommended as the best treatise upon the subject. G. W.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 25, No. 5, Boston Number). September, 1941. Philadelphia: W. B. Saunders Company, 1941.

THIS number features a symposium on methods of treatment in diabetes, pneumonia, pulmonary tuberculosis, common forms of heart disease, bacterial meningitis, migraine, epilepsy, exophthalmic goiter, peptic ulcer, gall bladder disease, nephritis and urinary tract infections. The issue also contains articles on infant feeding, the preventative aspects of military medicine, conditions simulating pulmonary tuberculosis and the clinical application of electro-encephalography.

The subjects are well presented, new methods as well as old being discussed, though some can scarcely be considered "specific." The majority of the articles discuss both diagnosis and therapy. The rôle of sulfonamide therapy in the various indicated diseases is properly evaluated in most instances, though the value of these drugs in subacute bacterial endocarditis is perhaps overrated. The article on diabetes contains valuable advice on its management in automobile drivers. In the section on the treatment of meningitis there is a great deal of repetition and, after ascribing a high incidence rate (first in some reported series) to tuberculous meningitis, the treatment of this disease is not discussed, perhaps because of the hopeless prognosis in this type. In the treatment of acute cholecystitis, the administration of only sodium chloride solution intravenously is recommended, though the value of glucose, in such cases is well recognized. In the discussion of the diagnosis of gall bladder disease, there is no reference to the examination of bile obtained by duodenal aspiration as a diagnostic procedure T. M.

WOUNDS AND FRACTURES. A Clinical Guide to Civil and Military Practice. By H. WINNETT ORR, M.D., F.A.S.C., Lincoln, Nebraska; Chief Surgeon, Nebraska Orthopedic Hospital. Pp. 227; 137 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, $5.00.

THIS book is in reality a monograph on Dr. Orr's method of treating fractures rather than the clinical guide that the title indicates. There is no question as to the brilliant results of the Orr methods of treatment in many cases, but it would be a mistake not to emphasize the fact that many fractures can be treated successfully without the use of pin fixation. In fact, it is doubtful whether the widespread use of pins should be encouraged.

The Reviewer also believes that infection in compound fractures may in part at least be combated by the use of sulfonamide therapy, but the use of this drug has not been mentioned by Doctor Orr. Does it not deserve a trial at his hands?

Aside from these two criticisms this volume deserves only praise for its exposition of this important method of treatment which has done so much to reduce mortality and morbidity in patients with compound fractures.

I. R.

SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE. By WESLEY W. SPINK, M.D., Associate Professor of Medicine, University of Minnesota Medical School. Pp. 256. Chicago: The Year Book Publishers, Inc., 1941. Price, $3.00.

THIS is the fourth book on sulfonamide chemotherapy which has come to the Reviewer's attention in as many years, indicating the tremendous interest in the subject as well as the rapid advances which have been and are being made. Second editions or new ones will no doubt be needed in the near future.

The present volume is remarkably down to date, with the latest reference dated July, 1941. The subject matter is dealt with in an orderly manner beginning with the historical development and general principles of therapy. This is followed by a discussion of the three principally used compounds, sulfanilamide, sulfapyridine and sulfathiazole, describing for each in detail the dose and methods of administration, treatment of especially important infections, contraindications and so forth. Several chapters are devoted to disease complexes such as pneumonia, meningitis, urinary tract infection, and to chemotherapy in dermatologic, surgical, and dental fields. There are good chapters on chemoprophylaxis and toxic manifestations. The final two chapters discuss the available knowledge on the two most recently introduced compounds, sulfaguanidine and sulfadiazine.

The book is of convenient size and is written in a simple, clear, concise manner. It is remarkably free from typographic or other errors. Numerous interspersed case reports with charts illustrate important points in therapy. The bibliography is well arranged, adequate, and contains over 400 selected references. The index is complete.

The book has a justifiable enthusiastic tone but is tempered with the right amount of conservatism to make it a valuable one for the profession.

H. R.

A MANUAL OF THE TREATMENT OF FRACTURES. By JOHN A. CALDWELL, M.D., Professor of Clinical Surgery, College of Medicine, University of Cincinnati; Director of the Fracture Service, Cincinnati General Hospital, Cincinnati. Pp. 150; 76 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, $3.50.

ON the jacket of this manual is the statement "A Plain and Simple Text;" to this might be added "Written with clarity, conciseness and

originality." Doctor Caldwell has emphasized principles of treatment, has shown standard procedures and has provided a guide to the literature so that any student or house officer can act in an emergency if he is familiar with this manual; but he will also be aware of the fact that more detailed instructions are available and that it will be of interest and benefit to him to go to the source for them.

This book is heartily recommended to any one interested in the treatment of fractures. I. R.

LECTURES ON WAR NEUROSES. By T. A. ROSS, M.D., F.R.C.P. Pp. 116. Baltimore: The Williams & Wilkins Company, 1941. Price, $2.00.

A VERY colloquial, simple and short description of neuroses intended for general practitioners in civilian life and medical officers in the army.

It is very loosely knit together with many illustrative cases. The author insists on the need for prompt psychotherapy by whatever medical officers are near in the earliest hours of a war neurosis, and he describes the surprisingly good results from crude emergency measures. He advises that long-standing cases be handled only by psychiatrists. E. B.

IMMUNIZATION TO TYPHOID FEVER. Results obtained in the prevention of typhoid fever in the United States Army, United States Navy, and Civilian Conservation Corps, by the use of vaccines: influence of antigenic structure and other biological characters of *E. typhosa* on the production of protective antibodies in the blood of immunized individuals: increases in protective antibodies in the blood following the use of a single small dose of vaccine for reimmunization purposes as compared with the use of three doses.

From the Research Laboratories of the Army Medical School, Washington, D. C. Investigations carried out under the general supervision of: COL. J. F. SILER, M. C., U. S. A.; LT. COL. GEORGE C. DUNHAM, M. C., U. S. A.; MAJ. DON LONGFELLOW, M. C., U. S. A.; LIEUT. G. F. LUIPPOLD, San. Corps Res., U. S. A. Special investigations carried out and coöperative assistance rendered by the following members of the staff of the Medical Department Professional Service Schools, Army Medical Center, Washington, D. C.: MAJ. H. R. LIVESAY, CAPT. DON LONGFELLOW, CAPT. C. P. CANBY, CAPT. F. B. WAKEMAN, CAPT. F. E. COUNCIL, MAJ. F. H. K. REYNOLDS, LT. COL. A. P. HITCHENS, CAPT. WILLIAM S. STONE, LT. COL. W. D. FLEMING, CAPT. J. R. WOOD, CAPT. J. H. MCNINCH, LT. COL. R. L. HOLT, CAPT. A. R. DREISBACH, and LT. COL. S. D. AVERY. (The Am. J. Hyg. Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 276; illustrated. Monogr. Ser., No. 17, Sept., 1941.) Baltimore: The Johns Hopkins Press, 1941. Price, $2.50.

A COMPILATION of the extensive investigations into the antigenic and immunizing properties of *E. typhosa* during the period of 1934–1940 is most timely. Although many phases of the experimental work were published elsewhere from time to time, this report presents the work in more detail. A historical review of the use of typhoid vaccine in the Army, Navy, and Civilian Conservation Corps is included. Detailed descriptions are given of the experimental investigations on the antigenic characteristics of strains of *E. typhosa*, on the ability of the various vaccines to bring about the production of protective antibodies, the duration of immunity subsequent to immunization with typhoid vaccine and the matter of revaccination.

Briefly the findings are that the strain of *E. typhosa* used in the production of vaccine should be one of high virulence, preferably it should have been freshly isolated from a human being, and also preferably, the colonies resulting from growth on agar should be of the "smooth" type. For initial immunization the standard method of three doses (1st dose 0.5 cc., 2d and 3d doses 1.0 cc. for adults) administered at intervals of 1 week should be followed (content of vaccine 1000 million *E. typhosa* per cc.). For reimmunization a single dose of a virulent type vaccine will result in adequate restimulation of antibody production. The single dose for reimmunization may be 0.5 cc. subcutaneously or 0.1 cc. intracutaneously, the latter method is to be preferred. Reimmunization should be carried out ordinarily between 2 and 3 years subsequent to initial immunization and this reimmunization should be repeated at least once at the end of another 2 to 3 years. H. M.

NEW BOOKS.

Abdominal Surgery of Infancy and Childhood. By WILLIAM E. LADD, M.D., F.A.C.S., William E. Ladd Professor of Child Surgery at Harvard Medical School; Chief of Surgical Service, The Children's Hospital, Boston, and ROBERT E. GROSS, M.D., Associate in Surgery, the Harvard Medical School; Associate Visiting Surgeon, The Children's Hospital; Associate in Surgery, The Peter Bent Brigham Hospital, Boston. Pp. 455; 268 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, $10.00.

Treatment of the Patient Past Fifty. By ERNST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City; Chairman, Committee on Chronic Illness, Welfare Council of New York City; Assistant Clinical Professor of Medicine, Columbia University. Pp. 324; 19 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, $4.00.

The March of Medicine. New York Academy of Medicine Lectures to the Laity, 1941. Pp. 154; 4 illustrations. New York: Columbia University Press, 1941. Price, $2.00.

The New International Clinics, Vol. IV, New Series 4, December, 1941. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 314; illustrated. Philadelphia: J. B. Lippincott Company, 1941.

In addition to 12 miscellaneous "clinics" from the University of Minnesota, and a 10-page progress review of The Surgery of Modern War, by Calvin M. Smythe, Jr., this number contains 11 "original contributions" from various sources on various subjects of greater and lesser importance and merit.

The 1941 Year Book of Pathology and Immunology. Pathology, edited by HOWARD T. KARSNER, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University, Cleveland. Immunology, edited by SANFORD B. HOOKER, A.M., M.D., Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals. Pp. 623; 136 illustrations. Chicago: The Year Book Publishers, 1941. Price, $3.00.

Hérédité Mendélienne et Analyse Combinatoire. By E.-L. ROULET. Pp. 193. Geneve: Georg et Cie, 1941. Price, Sw. Fr. 12.

Allergy in Clinical Practice. By Staff-Members of the Cleveland Clinic. Under the direction of RUSSELL L. HADEN, M.D., F.A.C.P., Chief of the Medical Division. Edited by J. WARRICK THOMAS, M.D., F.A.C.P., Chief of the Section on Allergy. Pp. 354; 92 illustrations (some in color). Philadelphia: J. B. Lippincott Company, 1941. Price, $5.00.

Behind the Mask of Medicine. By MILES ATKINSON. Pp. 348. New York: Charles Scribner's Sons, 1941. Price, $3.00.

Chinese Lessons to Western Medicine. A Contribution to Geographical Medicine From the Clinics of Peiping Union Medical College, Peiping, China. With a Foreword by GEORGE R. MINOT, Professor of Medicine, Harvard University. Pp. 380; 132 illustrations and 38 tables. New York: Interscience Publishers, Inc., 1941. Price, $5.50.

Language in Action. A Guide to Accurate Thinking. By S. I. HAYAKAWA, Assistant Professor of English, Illinois Institute of Technology. Pp. 245. New York: Harcourt, Brace & Co., 1941. Price, $2.00.

I'm Gonna Be a Father! By BOB DUNN (with a little assistance from his wife). 80 illustrated pages. Philadelphia: David McKay Company, 1941. Price, $1.00.

Intended for comic relief only.

The Doctors Mayo. By HELEN CLAPESATTLE. Pp. 822; illustrated. Minneapolis: The University of Minnesota Press, 1941. Price, $3.75.

Endotracheal Anæsthesia. By NOEL A. GILLESPIE, D.M., B.CH., M.A. (OXON.), D.A. (R.C.S. ENG.), Research Associate and Resident in Anæsthesia, University of Wisconsin; State of Wisconsin General Hospital, etc. Pp. 187; 44 illustrations and 1 colored plate. Madison: The University of Wisconsin Press, 1941. Price, $4.00.

The Laryngoscope. Its Use in the Diagnosis of Common Laryngeal Pathology, and in Examination of the Pharynx and Nasopharynx. Pp. 32; 27 illustrations (many in color). Southbridge, Mass.: American Optical Company, 1941.

Encephalitis. A Clinical Study. By JOSEPHINE B. NEAL, A.B., M.D., Sc.D., F.A.C.P., Associate Director, Bureau of Laboratories, Department of Health, New York; Clinical Professor of Neurology, College of Physicians and Surgeons, Columbia University, with six Collaborators. Foreword by HUBERT S. HOWE, A.M., M.D., Clinical Professor of Neurology, College of Physicians and Surgeons, Columbia University. Pp. 563; 16 illustrations. New York: Grune & Stratton, 1942. Price, $6.75.

Acute Alcoholic Intoxication. A Critical Review. By HENRY W. NEWMAN, M.D. Pp. 207; 7 figures. Stanford University, Calif.: Stanford University Press, 1941. Price, $2.50.

NEW EDITIONS.

Diseases of the Nervous System. Described for Practitioners and Students. By F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. (LOND.), HON. D.Sc., National University Ireland, Physician in Charge of the Neurological Department, University College Hospital, London; Physician to the National Hospital for Nervous Diseases, Queen Square; Neurologist to the Hospital for Tropical Diseases, London, and the Seamen's Hospital, Greenwich. Pp. 325; 32 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, $4.50.

Dental Materia Medica, Pharmacology and Therapeutics. By WALTER J. DILLING, M.B., CH.B. (ABERD.), M.P.S. (HON.), Professor of Pharmacology and General Therapeutics, School of Dental Surgery, Liverpool University, etc., and SAMUEL HALLAM, L.D.S., R.C.S. (ENG.), Honorary Dental Surgeon, Liverpool Royal Infirmary, etc. Pp. 348. Second Edition, revised. London: Cassell & Co., Ltd., 1941. Price, 13/6.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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CUTANEOUS BURNS.

SEVERAL excellent papers summarizing the recent work on burns have been published during the last few years, and it is not the purpose of this article to add another to that list. Rather, we will try to present a critical analysis of the status of the research and treatment of burns, no attempt being made to refer individually to all of the investigations which have contributed to the present concepts.

The cause of death after severe burns has long been the subject of much study and speculation. Many theories have been presented and disproved, many local applicants have been advocated and abandoned, and many tables of mortality statistics have been published—however, actual advancement in this study has been slow. It can be said that at present we do not yet know the best method of treating these injuries.

One difficulty arises from the great variation in reaction shown by individual patients. The more important variables which cause these differences are: *a*, the extent of the body surface involved; *b*, the depth of skin involvement; *c*, the particular region of the body affected; *d*, the different effects produced by the numerous etiologic agents; *e*, the age, sex, occupation and individual tolerance of the patient; *f*, the inhalation of flames, fumes or smoke at the time of injury; and *g*, the occurrence of various complications such as pneumonia, Curling's ulcer, and so on. Because of these variables mortality statistics are difficult to evaluate, and for this reason the current trend of clinical study has been toward a more thorough investigation of individual patients.

Stages of Reaction. Any discussion of the etiology of the clinical manifestations presented during the course of a burn is complicated by the differences in terminology and the classical division of the various

stages following the inception of the burn. For the sake of clarity Wilson's[39a] classification of the stages of burn will be used in the following discussion, not because it is the more accurate or more desirable but because it may be more easily moulded to conform with the ideas of other investigators. Wilson lists the following stages: 1, initial shock; 2, secondary shock; 3, acute toxemia; 4, septic toxemia; 5, healing; 6, death in any of the above stages.

1. *Initial or Primary Shock.* This condition, which arises almost immediately after injury, is characterized by low blood pressure and has been considered to be due to vasomotor changes. It is probably produced by pain and fright since Underhill, Kapsinow, and Fisk[37] have demonstrated that it is not present when animals are burned under the influence of an anesthetic agent. Primary shock can usually be controlled in part by early adequate doses of morphine with supportive therapy, and care should be taken that the patient is past this stage before extensive local treatment of the burned area is started. Failure to realize this may lead to prolongation and intensification of the initial period of shock.

2. *Secondary Shock.* Underhill and his coworkers[36] as well as Robertson and Boyd[29a,b] regarded secondary shock and acute toxemia as belonging to the same stage; however, in the light of recent investigation less confusion will result if these two stages are kept separate and the second stage of burns (secondary shock) referred to as the "period of hemoconcentration."

Cumin [11]in 1823 was the first to note a thickening of the blood after severe burns as he stated that bleeding was difficult because the blood was "sizy." Underhill, Carrington, Kapsinow, and Pack,[36] 100 years later, demonstrated a marked hemoconcentration in patients with severe burns. Experimental work by Underhill, Kapsinow, and Fisk[37] demonstrated in animals that the burning of one-sixth of the body surface caused a loss of 70% of the total blood volume into the burned area, and analysis of this fluid showed it to be similar to blood plasma. Experiments by Blalock,[8a] Beard and Blalock,[4] Harkins,[17a,b] and others have confirmed this concept. The physiologic mechanism has been shown to be an increased capillary permeability in the burned area with a resultant rapid loss of plasma into this area occurring for the most part during the first 24 hours after injury. More recent studies demonstrate that a portion of the loss in plasma volume is from the surface of the burned area.

The clinical picture of this condition is one of hypotension, circulatory failure, and in severe cases, death. In fact the highest mortality occurs during this period. Hemoconcentration is easier to prevent than relieve. Parenteral fluid, especially plasma, should be started early since hemoconcentration increases most rapidly during the first 6 hours after injury. Weiner, Rowlette, and Elman[38] have emphasized the fact that large doses of parenteral saline are to be avoided since this frequently lowers the serum protein to an edema level, and the administration of large amounts of neutral sodium salts intensifies the edema at any given level of the serum protein. Wilson[39b] also warned against large volumes of saline and glucose, and stated that he found gum acacia valuable in controlling hemoconcentration without lowering the level of the plasma protein. Since hepatic injury is often associated with an extensive burn this procedure is, we believe, attended with

some danger. The value of plasma administration has also been stressed by McClure,[25] by Elkinton, Wolff, and Lee,[14] by Tenery[35] and Black.[6] Ideally, the plasma lost into the burned area should be replaced volume for volume with plasma, but this is neither practical nor always necessary. We have found that most cases with 30% to 40% of the body affected with a first and second degree burn will do quite well when given 1000 to 3000 cc. of plasma plus not more than 1500 cc. of a 5% glucose solution in saline during the first 24 hours, if the oral intake of fluid can be kept up so that the urinary output is from 800 to 1000 cc. After this initial period, therapy should be dictated by following the hematocrit, plasma protein, and plasma chloride concentrations. The plasma replacement is best done slowly, for the administration of large amounts of plasma in a short time increases the loss of protein from the vessels.

3. *Acute Toxemia.* As no toxemia has been definitely demonstrated, it would perhaps be more accurate to refer to this as the "toxic stage of burns." Tissue toxins, bacterial toxins, and hemoconcentration have all been suggested as the etiologic factor in this stage. With adequate therapy, primary shock, hemoconcentration, and infection can be prevented or controlled—yet, the patient may still develop, usually 48 to 72 hours after the burn, a syndrome characterized by lowered blood pressure, tachycardia, hyperpyrexia, malaise, increasing lassitude, delirium, coma, circulatory failure, and, in some cases, death. This has led many investigators to further search for a toxic agent.

It is the etiology of this clinical picture which has long been the center of burn investigation. Excellent reviews of this problem have been published by Harkins,[17c] Blalock,[8b] and Gunn and Hillsman.[15] Underhill believed that hemoconcentration accounted for the clinical picture seen in this stage, and Aldrich[1a] feels that the absorption of bacterial toxins is the most important factor; however, as pointed out above, this syndrome may develop in the absence of hemoconcentration and infection. It has been noted when plasma replacement was sufficient to prevent hemoconcentration and hypotension had not taken place.

Much evidence has been presented to show the existence of a toxin formed in the burned area. Much of the older investigation along this line has been refuted; however, the work of Wilson, and of Rosenthal, has yet to be confirmed or condemned. Wilson, Jeffrey, Roxburgh, and Stewart[40] in 1937, using rabbits, found that the edema fluid gradually became toxic, the potency being greatest after 48 hours after burning. This they attributed to autolysis of the injured tissue since culture indicated that bacteria played no rôle in this reaction. This late formation of a toxic material may explain why some previous investigators had found a toxin and others had not. Wilson,[39b] however, stated that the existence of such a toxin has not yet been definitely proved. Also in 1937 Rosenthal[31a,b] reported experiments in which he had found in the blood of burned animals a histaminoid substance which caused contraction of the virgin guinea pig uterus. This substance and histamine were both neutralized by the sera from experimental animals and humans in the healing stage of burns. Even normal sera neutralized these substances to a slight extent.

The work of Underhill, Kapsinow, and Fisk[37] indicated very little or no absorption of certain dyes and strychnine from the burned area

during the first 24 hours after injury; however, this need not indicate the lack of the later absorption of a toxin since this material is apparently not of great potency until about 48 hours after burning. The toxic stage usually does not appear until sometime after the first 24 to 48 hour period. Mason, Paxton, and Shoemaker[24] found that certain substances of low molecular weight such as sodium iodide, are quickly absorbed from the burned area in the first 24 hours, and Hooker and Lam[18] have demonstrated the same result with sulfanilamide. The toxin may have a higher molecular weight and absorption may then be similar to the materials used in Underhill's experiments.

Recent blood electrolyte studies in burns have been of some interest. As early as 1926 Davidson[12b] reported a lowering of the serum chlorides and evidence of a chloride retention which he suggested may lie in the tissues. Wilson and Stewart[41] found a marked decrease in the serum sodium level which generally followed the severity of the patient's condition; the administration of desoxycorticosterone acetate was followed by elevation of the plasma sodium and with clinical improvement in the patients. They also noted some increase in the serum potassium level following severe burns but made little comment on this finding. Scudder[33] reported a study of plasma potassium levels on 6 patients following the Hindenburg disaster in whom he found elevation of plasma and whole blood potassium; he employed adrenal cortical hormone in the therapy of these cases with apparent success. Keeley, Gibson, and Pijoan,[20] however, found no elevation of serum potassium in dogs which were burned. Black[6] has reported the finding of slight increases in chloride and potassium concentrations with lowering of the bicarbonate and sodium. Tenery[35] has studied the blood electrolytes in 8 severely burned patients, 3 of whom died. In these cases the plasma potassium rose slightly, the plasma chloride gradually fell, and the plasma sodium decreased markedly in spite of parenteral saline. The plasma potassium did not reach a toxic level, and the changes in the sodium level did not follow the clinical course. Since 6 of these patients showed evidence of the toxic stage, it was concluded that changes in blood electrolytes are not responsible for the toxic stage, though they must be considered in the general therapy of the patient. Harkins[17c] and Tenery emphasized the fact that determinations of whole blood electrolytes in cases of severe burn are of little aid since these values will vary with changes in the hematocrit because of the difference between plasma and cellular concentrations. Lam[21] has recently presented an excellent review of the literature on the blood chemical changes found in burns.

4. *Septic Toxemia.* This stage is generally admitted to be due to bacterial infection of the burned area, frequently with hemolytic streptococci; it is thought to begin when the temperature curve starts a septic swing, though Aldrich[1a] believes that it starts much earlier. In the past, infection of the burned area was the common and expected occurrence, but at present is becoming less frequent.

This brings us to one of the most controversial subjects in the study of burns, namely, the treatment of the burned area.

Local Treatment. Almost everything in and out of the pharmacopeia has been used in the local treatment of burns. Because of the many variations presented by each individual case, the evaluation of these

agents is most difficult. Mortality statistics are even less reliable than data obtained from a study of the systemic changes.

The methods of local treatment in use today can be divided into four main types: 1, eschars; 2, wet dressing or submersion; 3, dressings with various agents which do not form eschars; 4, immediate skin grafting of the third degree burns.

1. *Eschars.* Certainly the introduction of tannic acid by Davidson[13a] in 1925 was the greatest single advance in the treatment of burns, but this method has been greatly misused in that many have applied tannic acid to every burn regardless of the extent, depth, or location of the lesion. One has only to apply an eschar to the face on a single case of burn to learn that this can cause almost unbearable pain with every slight movement of the facial muscles. After the first 2 or 3 days, following injury the patient becomes truly "The Man in the Iron Mask." Likewise an eschar applied around the anus is apt to become infected and require removal. This is not a condemnation of the eschar treatment of burns. At present it is the most convenient method of handling a large body burn; however, any eschar has the disadvantage of not being the most applicable method for permitting early skin grafting.

Tannic acid alone has several disadvantages, the more important of which are: 1, the coagulum is brittle and tends to crack over areas subjected to bending, thus allowing bacteria to enter beneath the coat; 2, the eschar is quite stiff and tends to pull away and curl in at the edges and thus allows infection to enter; 3, the eschar is dense and fluid-proof so that underlying infection is at times masked; 4, several hours and many applications are required to form the coagulum.

With these disadvantages in mind and in an effort to eliminate infection, Aldrich presented the gentian violet[1a] and later the triple-dye[1b] treatments. This method eliminates all except the fourth disadvantage of tannic acid. Bettman[5] advocated the use of tannic acid plus silver nitrate as this forms an immediate eschar which is, if properly and promptly applied, more pliable than when tannic acid is used alone. Branch[9] then recommended the use of gentian violet with silver nitrate which makes a more pliable coagulum than that advocated by Bettman. Other eschar-forming agents advocated in the past are ferric chloride, horse serum, and picric acid. This latter is an excellent agent except for the disadvantage that too many individuals are sensitive to the drug.

The more recent addition to the list of eschar-forming agents is sulfadiazine in triethanolamine[28] which is said to produce a transparent, pliable eschar with the high antiseptic value of the sulphonamides. This treatment offers some promise, although it has the great disadvantage of requiring frequent applications over a long period before an eschar is obtained. Pickerell states that preliminary cleaning with soap and water is unnecessary before application of the solution, but this might prove to be unwise. This method has not been subjected to the wide application as have other agents and needs further study before general adoption.

2. *Wet Dressings.* In 1858 Passavant[26] introduced the continuous submersion treatment; he advocated the use of a tub of water to be changed 3 times daily. Blair, Brown, and Hamm[7] in 1932 recommended the use of a daily tub bath of hypertonic saline, physiologic saline, or water. Lavender[22] advised daily submersion in dilute green

soap solution with wet dressings of Burrow's solution during the intervals. The use of such baths continuously for the first few days after burning is valuable but has the disadvantage of requiring special equipment if many cases are to be handled. Darrow[12] has suggested that continuous or frequent bathing in hypotonic solutions may deplete the body of sodium chloride as the raw surface permits diffusion into the water. Salt solution should be used to obviate this difficulty. Wet dressings with physiologic saline solution are especially useful on hand and face burns and on burns that will require early grafting; however, this procedure requires added nursing care. Saline compresses are of undoubted value in the treatment of infected burns.

Bunyan[10a,b] has made use of coated silk envelopes which are sealed around the upper portion of burned extremities; and irrigation with electrolytic sodium hypochlorite solution is carried out 3 times daily through openings into the envelope. This treatment allows free movement of the hands and feet and makes possible frequent inspection without the painful procedure of removing dressings. Bunyan has also devised coated silk coverings for treatment of other portions of the body. Hudson,[19] Hannay[16] and Pearson, Lewis and Niven[27] have all reported excellent results by the use of the envelope on burns of the extremities. The method could be used without the hypochlorite solution by substituting physiologic saline solution, with or without sulfanilamide.

3. *Dressings With Agents Which Do Not Form Eschars.* In 1914 Barthe de Sandfort[3] introduced the paraffin wax treatment and this was in vogue until the introduction of tannic acid. Recently, there has been a trend to return to "greasy" applications. This has come about through the knowledge that the most virulent infections occur after the initial dressing and can be prevented if care is taken to prevent subsequent contamination. A definite advantage of this type of dressing is that it can be easily removed for early skin grafting of third degree burns. The essential technique of this method consists of covering the wound with an ointment, gauze, and protective dressing after making the wound surgically clean by washing with soap and water; the inner layer of gauze should then be left in place 7 to 14 days unless evidence of infection appears.

After a thorough cleaning of burns of the hand, Allen[2] uses plain vaseline gauze with a voluminous gauze pressure dressings and splints. MacCollum[23] emphasized the point that an eschar on burns completely encircling the fingers may impair circulation since it does not allow for swelling of the fingers. For this reason he recommended an ointment gauze dressing especially for this type of burn. Steel[34] and others have advised cod-liver oil dressings because of the supposed vitamin stimulation of epithelization. It is still questionable whether this does any good.

The use of sulfadiazine in triethanolamine covered after the first application with sulfadiazine ointment gauze[28] may offer a satisfactory method of treatment. Robson and Wallace[30] have recommended the use of glycerin-sulfonamide-kaolin paste. Pearson, Lewis, and Niven[27] report excellent results on face burns by the use of sulfanilamide powder covered with tulle gras.

After preliminary cleaning of infected burns of the extremities Roulston[32] has covered the involved area with vaseline gauze and

enclosed the extremity in a plaster mold; he reports excellent healing, freedom from pain, subsidence of infection, and no added limitation of joint motion when the plaster is removed.

4. *Immediate Skin Grafting.* This procedure has a definite place in the treatment of small third degree burns as it will give the most rapid and best cosmetic result with a minimum of contracture. However, it is not always possible to know immediately which burns extend deeper than the hair follicle and sebaceous glands. It inflicts additional trauma in the extensively burned patient who is shocked and may soon enter the toxic stage and therefore should be reserved for those patients with small burned areas who are in excellent shape.

5. *The ideal local treatment* of burns should fulfill all of the following criteria:

1. Bacterial contaminants should be removed, destroyed, or their growth inhibited.
2. Subsequent bacterial contamination must be prevented.
3. The treatment should be carried out with a single, non-shocking procedure so that disturbance of the patient will be minimal while the systemic reaction is most severe.
4. The material applied to the burned area should not damage the living cells remaining, nor should it be toxic if absorbed in the quantity necessary to cover any given burn.
5. The burned area should be protected against trauma from brushing the bedclothes, and so on.
6. The covering should not mask underlying infection.
7. The covering should be easily removed so that early grafting can be carried out in the more extensive burns.
8. The covering should require a minimum of attention and should facilitate rather than hinder nursing care.

From the above one can see that there is still no ideal treatment which can be applied to all burns. Each case must be considered separately as an individual problem and one's armamentarium should include several types of treatment. It is important that cleaning the area with soap and water and débridement of loose tissues should be carried out in all cases. This procedure can be done on most patients with the aid of narcotics alone, although occasionally general anesthesia may be required.

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OPHTHALMOLOGY.

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OCULAR LESIONS IN THE SARCOIDOSIS OF BOECK.

It is assumed commonly that the various forms of involvement of the uveal tract, iritis, iridocyclitis, uveitis, choroiditis, are local manifestations of some systemic disease. The determination of the nature of the responsible systemic disease in the individual case frequently is quite difficult and taxes the diagnostic powers of both ophthalmologist and internist. Certain local features of the ocular disease may arouse the suspicion of a specific etiology. Thus, most cases of iridocyclitis which present nodules in the iris are suspected of being tuberculous. However, all cases of tuberculous iritis do not present nodules in the iris and all nodules in the iris are not tuberculous in origin. Therefore, to reduce as far as possible the number of cases of uveal disease in which the etiology is not determined, it is necessary for the ophthalmologist and the consulting internist to be familiar with the rarer as well as with the more common systemic causes of involvement of the uveal tract. For this reason, it seems worth while to call attention to the ocular manifestations of the systemic distribution of sarcoidosis which too frequently is thought of as a disease essentially of the skin.

Longcope and Pierson[11] stated that the lesions of sarcoidosis are described in the literature under a great variety of names, such as "lupus pernio" (Besnier), "sarcoid" (Boeck), "benignes miliar lupoid" (Boeck), "Boeck's sarcoid," "benign lymphogranulomatosis" (Schaumann), "ostitis tuberculosa multiplex cystoides" (Jüngling), "maladie de Besnier—Boeck," and "Hutchinson-Boeck's disease." The most characteristic features of the disease as listed by Longcope and Pierson are, in the skin, firm red, violaceous, or brownish swellings usually well demarcated from the surrounding skin; in the lungs, roentgenographically, enlarged peribronchial lymph nodes, increased hilar shadows, a marbled reticulated appearance of the lungs resembling miliary tuberculosis or pneumoconiosis, the infiltration extending, however, from the roots of the lungs toward the bases rather than toward the upper lobes and apices; in the bones, roentgenographically, areas of rarefaction and reticulation distributed through the medulla of the phalanges of the hands and feet, sometimes with irregular enlargement and distortion of the bones but without involvement of the periosteum or joints, these changes being expressed clinically in some cases by irregular enlargement of the fingers, dorsal flexion of the last phalanx and subcutaneous nodules around the interphalangeal joints; and in the eyes, iritis or iridocyclitis and nodules in the conjunctiva. Practically any organ or tissue of the body may be involved, so that generalized enlargement of the lymph glands and of the salivary and lacrimal glands may be seen, the spleen and liver may be enlarged, and the mucous membranes of the nose, nasopharynx and larynx may be involved. In essence, the disease seems to be, as summarized by Longcope and Pierson, a chronic infectious granuloma, insidious in onset, persisting often for years, sometimes spreading slowly from one organ or tissue to another, frequently relapsing, seldom producing serious constitutional symptoms, resistant to treatment but at times healing spontaneously. In King's[9] opinion, "Boeck's sarcoid is a generalized granulomatous disease involving primarily the lymph nodes, the lungs, the bone marrow, and the spleen. When the skin, the eye and other organs are involved, the condition may be regarded as secondary." Histologically, the characteristic lesion found in tissue removed for biopsy from the skin or lymph nodes is the so-called hard tubercle, a collection of large, poorly-staining epithelioid cells with a scanty marginal zone of lymphocytes, with a few giant cells of the Langhans type, and without caseation. Little direct proof can be furnished through skin tuberculin tests, through the demonstration of tubercle bacilli in the lesions, or through guinea pig inoculation studies that the lesions are truly tuberculous. In the few cases that have come to necropsy, death has been caused apparently by miliary tuberculosis and the consensus seems to be that the disease is a peculiar benign form of tuberculosis. However, Snapper expresses his own opinion and that of several other students of the disease to the effect that "Besnier-Boeck's disease must therefore be considered as a peculiar reaction of the reticulo-endothelium with formation of pseudotubercles under influence of an unknown virus."

In most of the earlier reported cases of sarcoid the skin lesions were regarded as the primary if not the sole manifestations of the disease. It might be expected that the external structures of the eye would be involved rather frequently. However, only a few cases of sarcoid of

the eyelids, of the conjunctiva, and of the orbital tissues have been reported. In 1917, Derby and Verhoeff[4] reported the removal of a small painless growth which was situated in the outer third of the lid and ran upward and inward under the orbital margin. Histologic examination proved this growth to be a sarcoid. One discrete nodule of the same type was present on the cheek, but no mention was made of the presence of sarcoids in other parts of the body. At that time, Derby stated: "I have been unable to find in ophthalmic literature any reference to sarcoid, and in a fairly extensive search in the literature of the disease I have not happened upon a case where involvement of the ocular structures was noted." In 1937, Ernsting[5] reported an almost identical growth which proved on removal to be a sarcoid of the Boeck type. This patient had Roentgen ray evidence of hilar gland enlargement and of sarcoid type infiltration of the lungs and also erythematous lesions on the anterior surfaces of the lower legs which proved on biopsy to be sarcoids of the Darier-Roussy type. Ernsting stated that Lehrfeld reported a case of sarcoid of the eyelid in 1927 and that Friede, Coppez, and Blegvad had reported cases of conjunctival involvement. Blegvad[2] stated that he could find records of only 8 cases, including 3 of his own (1930). Blegvad described the lesions as small to large chalazion-like tubercles, one to many, studding the conjunctiva, or else clear yellowish speck-like follicles. In 1925, Igersheimer[8] reported symmetrical tumors of the tarsal conjunctiva of both lower lids which had the histologic structure of Boeck's sarcoid. He stated that Schoeppe had described in this disease small glossy nodules in the ocular and tarsal conjunctiva with small nodules in the tarsus itself and in the iris. In 1939, Walsh[23] stated that "sarcoid of the eyelids has been described frequently. In this situation sarcoid may or may not be associated with involvement of the adjacent tissues, such as conjunctiva, extraocular muscles or orbital tissues." He did not present references to support this statement but includes as an example of sarcoid a case which had been reported by Wilmer in 1933 under the title "Tubercle-like nodules of the episclera and eyelids, bilateral." The patient, a woman, aged 56, presented painless, freely-movable lumps in the eyelids and a mass in the subconjunctival tissue over the right internal rectus muscle. Within $2\frac{1}{2}$ months all the masses had disappeared spontaneously with the exception of one in the lower lid of the right eye. This was excised and showed the histologic picture of "hard tubercle" characteristic of sarcoid. In 1 of the 7 cases of sarcoidosis reported by King, a small firm nodular mass under the conjunctiva projecting into the lower fornix from behind the globe proved histologically to be Boeck's sarcoid. In another case with bilateral kerato-iritis, a sarcoid was found in the skin of the eyelid. Recently (1941), Rosenbaum[16] and Sniderman[20] have each reported a case of histologically proven Boeck's sarcoid of the lacrimal glands. In Rosenbaum's case there was enlargement also of the cervical and inguinal lymph nodes. In Sniderman's case there was also bilateral uveitis and enlarged hilar glands by Roentgen ray.

Perhaps of more general interest than these rather isolated instances of involvement of the external ocular structures with growths or nodules of sarcoid type are the lesions of the uveal tract which can be demonstrated to be a part of the disseminated picture of sarcoidosis. King

stated that iritis occurs in 10% of the cases of Boeck's sarcoid. In their monograph, Snapper and Pompen[19] stated: "One of the favorite sites of the disease is the eye; here dissemination of nodules in the iris and in the corpus ciliare explains the frequency with which symptoms of iridocyclitis are found in these patients. As a matter of fact, many of them first consult ophthalmologists and are diagnosed as tuberculous iridocyclitis. Careful general examination may then reveal the presence of other manifestations of Besnier-Boeck's disease. Not uncommonly small nodules of Boeck's disease can be discovered in the conjunctiva in the form of typical yellowish brown nodules." In the series of 13 cases reported in this monograph, iridocyclitis was noted five times, conjunctival nodules twice, and recurrent hemorrhages into the vitreous once.

According to available statistics the actual number of cases of "sarcoid iritis" is not very great. King stated that Osterberg found 26 cases of iritis among 400 cases of Boeck's sarcoid. King noted also that in the $6\frac{1}{2}$ years preceding the publication of his paper, over 1700 patients with various forms of chronic ocular inflammation had been tuberculin tested in the Howe Laboratory. In about two-thirds of the patients, the tests were positive. Among the remaining one-third of cases insensitive to tuberculin (amounting then to between 500 and 600), 7 cases were diagnosed as Boeck's sarcoid. However, the relative infrequency with which cases of iritis or uveitis associated with sarcoidosis are reported in the ophthalmologic literature may well be accounted for by the suggestion contained in the remark of Snapper and Pompen that most of these cases are diagnosed by ophthalmologists as tuberculous.

Some authors believe that the clinical appearances of tuberculous iridocyclitis and of sarcoid iridocyclitis are identical with small nodules in the iris, cloudy media, precipitates on the posterior surface of the cornea, and tendency to the development of posterior synechiæ, secondary glaucoma and complicated cataract. Osterberg thinks that, in general, the iritis of Boeck's sarcoid is less painful, less destructive and less proliferative than tuberculous iritis, but that individual cases are difficult to differentiate. Blegvad states that iritis occurs in association with Boeck's sarcoid in one of two forms or phases, the serous or the nodular. In the serous phase, the iritis has no special characteristics other than its frequent association with band-shaped keratitis. The nodular phase or form, however, has characteristics which should distinguish it from tuberculous iritis. Tuberculous nodules in the iris are dirty white or slightly yellowish, almost always quite round or oval with smooth surfaces, and appear to come from deep in the iris, shoving aside the surface fibers. Vessels go around the nodules. When they resolve, residual spots of atrophy of the iris tissue remain. The nodules of Boeck's sarcoid are often very large, are not smooth and round but have an irregular surface, are reddish-yellow in appearance and are traversed by a number of fine branching vessels. They are apparently firmer and harder than tuberculous nodules and may proliferate through the sclera at the limbus. They have a spontaneous tendency to heal and disappear without trace, leaving no residual atrophy of the iris.

King also notes the two types of iritis in sarcoidosis. He states that the serous type is characterized by slight ciliary injection, fine posterior

corneal precipitates and a moderate amount of cells in the aqueous. In the nodular type, the ciliary injection is more marked, the cornea is usually edematous and cloudy, the precipitates on the posterior surface of the cornea are larger and more numerous. In the iris, the nodules are apt to be few in number, are fairly discrete and are invaded by blood-vessels. They are smaller and more superficially situated than the nodules of tuberculous iritis. The clinical course is usually more benign than in tuberculous iritis and healing may occur with complete resolution of the nodules and often with little scarring and slight impairment of vision. However, the course of the iritis may be complicated by corneal opacification and the development of posterior synechiæ and secondary glaucoma. In King's opinion it is difficult to distinguish clinically between the ocular lesions produced by Boeck's sarcoid and by tuberculosis, and the differential diagnosis depends usually on the identification of the disease process elsewhere in the body, biopsy of skin or lymph nodes, roentgenographic studies of the chest and bones, serologic studies and tests for allergy. Occasionally, the diagnosis is confirmed, as in one of King's cases, by histologic study of a portion of the iris removed by iridectomy for the treatment of secondary glaucoma. In summary, King states that, "When characteristic changes are revealed by biopsy of the skin, lymph nodes, or bone, and by *x*-ray; when the Wassermann and tuberculin tests are negative and the constitutional symptoms are relatively slight, a diagnosis of sarcoid becomes as nearly positive as it can be with our present knowledge."

Only occasional reports of involvement of other tissues of the eye in cases of Boeck's sarcoid have appeared in the literature. Chorioretinitis has been mentioned occasionally but usually in association with iridocyclitis. King mentioned the finding in sections of an enucleated eye, which he examined in conjunction with Verhoeff, typical sarcoid nodules in the retina and in the distal portion of the optic nerve. In 1935, Salvesen[17] reported bilateral optic neuritis in a patient with Boeck's sarcoid of the skin of the arms, infiltration of the hilus glands, renal insufficiency, fever, increased sedimentation rate, achylia, secondary anemia, and negative Wassermann and skin tuberculin tests. The optic disks were grayish-red, blurred, and elevated 1 D. Vision was reduced to hand movements. Nine months later the disks were pale and the vision was 5/10 in the right eye and 5/30 in the left eye. In 1938, Roos[15] reported the case of a girl, aged 6 years, with bilateral uveitis and benign lymphogranulomatosis, the diagnosis being established by biopsy of a lymph node. Later, there developed bilateral choked disks of 1 D, drowsiness, three attacks of generalized convulsions, and transient paresis of the right arm and leg. The spinal fluid was under increased pressure and contained increased cells and protein. The girl's condition improved gradually.

In 1931, Reis and Rothfeld[14] described the case of a 17-year-old girl with headache and vomiting, skin sarcoids of the Darier-Roussy type (confirmed by histologic examination), negative Wassermann, negative von Pirquet and Mantoux tests, and roentgenographic evidence of osteitis cystica tuberculosa (Jüngling) and of enlarged hilus glands and of infiltration of the apex of the right lung. There was bilateral exophthalmos greater in the left eye. The vision was ability to count fingers at 16 inches in the right eye and *nil* in the left eye. Ophthalmoscopic

examination revealed in the right eye a choked disk of 5 D with secondary optic atrophy and in the left eye a white tumor mass occupying practically all the retina under the retinal vessels and projecting 20 D into the vitreous. There was slight weakness of the right leg and bilateral positive Babinski's. The spinal fluid showed increased protein. Later, the patient developed loss of memory and mentality and epileptiform convulsions and died in an epileptiform attack. Necropsy revealed at the base of the brain a flat, translucent, yellowish, hard infiltration around the infundibulum, chiasm, and both optic nerves, extending back to the cerebral peduncles and laterally under the temporal lobes, greater on the left. The floor of the third ventricle was markedly infiltrated. Generalized tuberculosis in various stages was found in other organs and tissues. The left optic nerve was markedly enlarged, the sheaths edematous and matted together with local infiltrations of small cells and proliferation of connective tissue with some blood-vessels. The walls of the blood-vessels showed hyaline degeneration or infiltration with lymphoid cells. There were several varying-sized foci of epithelioid cells with marginal zones of lymphocytes without giant cells, necrosis or caseation. The tumor mass consisted apparently of tuberculides somewhat altered by edema.

One of the patients in a series of cases reported by Walsh in 1939 showed, in the right eye, slight pallor of the disk with numerous superficial discrete white dots in the paramacular area with a tendency to perivascular arrangement, and in the left eye, uveitis with marked atrophy of the optic nerve and white spots scattered throughout the fundus. There were bitemporal field defects, but a normal sella. One year later, a mass elevated 8 D was present in the choroid of the left eye. It was considered to be tuberculous. Nine years later there was marked optic atrophy in the right eye with contraction of the temporal part of the field of vision; the left eye was phthisical. The patient had developed diabetes insipidus, but roentgenographs of the head were still normal. The left eye was enucleated and the mass in the choroid proved histologically to be a sarcoid tumor. Walsh also mentioned a case of Vandergrift's, as yet unreported, with bilateral papilledema and sarcoid masses in the brain and meninges.

Aside from the cases mentioned above, there are very few reports of involvement of the nervous system in association with Boeck's sarcoid. According to Roos and Salvesen, Boeck himself mentioned the presence of anesthesia over the ulnar distribution in one arm of one of his patients; Nazza mentioned pain, loss of sensation, muscular paresis and atrophy in the arms and legs proved at necropsy to be due to sarcoid nodules in the nerves; Urban and Winkler found infiltrations around the cutaneous nerves.

Perhaps more frequent in occurrence than the typical "sarcoid iritis" and certainly more frequently reported in the literature are cases of so-called "uveoparotid fever," "uveoparotid tuberculosis," "uveoparotitis" or "Heerfordt's disease." As stated by Longcope and Pierson, the syndrome of uveoparotid fever consists of bilateral uveitis and parotitis preceded or accompanied in the early stages by fever. Later, the disease becomes chronic, the fever usually subsides and other symptoms appear. After many months, recovery usually takes place. Paralysis of the facial nerve is said to accompany the swelling of the

parotid gland in about one-third of the patients, and in one-half of these the facial paralysis is bilateral. Pareses of other cranial nerves may occur or more distant parts of the nervous system may be affected. There may be swelling of the submental, submaxillary and cervical lymph nodes. Occasionally, there are associated skin lesions of varying types, including erythema nodosum. In a few cases, roentgenograms of the chest show increased shadows in the mediastinum or at the roots of the lungs.

Most of the articles on the subject of uveoparotid fever present essentially reports of one or a few cases. However, Savin[18] presents an analysis of the symptoms and findings in 67 cases. The two sexes are almost equally affected and the disease can occur at essentially any age, though it appears most commonly between the ages of 10 and 30. It starts usually with parotid swellings or iritis, but the initial symptom may be a facial or other paralysis or erythema nodosum. The parotid swellings are painless, may last from 6 weeks to 2 years, and do not suppurate. The iritis is at times nodular in type and precipitates on the posterior surface of the cornea are present frequently. Occasionally conjunctivitis is present and, rarely, transparent nodules are found on the ocular and palpebral conjunctiva. In some cases, keratitis has been reported, in 7 cases optic neuritis, in 10 cases opacities in the vitreous and in a few cases choroiditis and hemorrhages in the retina. Facial paralysis occurred in 20 cases and was bilateral in 9. In scattered cases, ptosis, diplopia, paralysis of the soft palate and of the recurrent laryngeal nerve, and polyneuritis of the peripheral type have been reported. Fever was present in 16 cases, erythema nodosum or other skin lesions in 16 and pulmonary tuberculosis in 10. The facial palsy so common in these cases may or may not be due to pressure on the nerves by the parotid swelling. That it is not is suggested by the order of occurrence of the lesions in a case reported by Muirhead.[13] First, iridocyclitis with secondary glaucoma of the right eye; 2 months later, iridocyclitis of the left eye; 2 weeks later, right facial palsy; 2 months later, left facial palsy, and 1 month later, bilateral parotitis. According to Tait,[21] the uveitis is insidious and painless in its onset. It is characterized by the production of a typically adhesive exudate, readily producing posterior synechiæ of considerable strength and permanency. There are profuse coarse deposits on the posterior surface of the cornea. The vitreous may contain numerous opacities. Secondary glaucoma may develop. In other cases, the iritis may be of nodular type. McCulloch[12] states that the nodules in the iris are small, pale and gelatinous-looking and occur usually at the pupillary margin or on the collarette, occasionally at the ciliary margin.

Arbuse and Madonick[1] list the symptoms of uveoparotid fever under five headings: 1, prodromal—general malaise, weakness, lassitude, drowsiness, anorexia, gastro-intestinal upsets, loss of weight, puffiness of eyelids, long-continued dryness of mouth, dysphagia, cough, night-sweats, pain in the chest, abdomen or joints, paresthesias, polyuria without glycosuria, paralysis of other cranial nerves besides the facial, low-grade temperature; 2, glandular—involvement of the parotids, painless, non-suppurative, is constant; at times enlargement of the

submaxillary, sublingual, lacrimal, cervical and hilar glands; 3, ocular—involvement of the eyes is always present but may vary in type; iritis, cyclitis, or uveitis usually, conjunctivitis, corneal herpes or other forms of keratitis, opacities in the aqueous or vitreous, chorioretinitis, hemorrhages in the retina, optic neuritis or atrophy, neuroretinitis, glaucoma (secondary), and cataract (complicated) occasionally; (4) neurologic—50% of the cases present some abnormality of the nervous system; facial paralysis is most common; peripheral neuritis, ptosis, involvement of the sensory part of the fifth nerve, dysphagia, loss of taste, hallucinations, meningeal signs, delirium, hypersomnia, convulsive seizures may occur; the spinal fluid may show an increase in cells and protein content; 5, other manifestations—diabetes insipidus, erythema nodosum, xerodermia, papulonecrotic tuberculides, polyarthritis and amenorrhea may occur; the electrocardiogram may indicate myocardial involvement.

Levin[10] listed the neurologic manifestations of uveoparotid fever as follows: edema of the optic disks (at times), partial ptosis, diplopia without complete oculomotor paralysis, involvement of the fifth nerve (sensory portion), the seventh (most common, a peripheral type of neuritis not always due to parotid swelling), the eighth, the ninth or the tenth nerve, peripheral neuritis, diabetes insipidus (rather frequent), hypersomnia, pyramidal tract involvement (1 case), ataxia, headache and vomiting, mild increase in the cell and protein content of the spinal fluid. He stated that the usual course of the disease is toward gradual recovery with postiritic residuals.

This, then, would seem to be a disease with protean manifestations, there being only two requisites for the inclusion of a case in the group, parotitis and some form of ocular involvement, usually uveitis. At the outset, Heerfordt's disease was considered to be a distinct entity in itself, but, recently, it is being recognized more and more widely that so-called "uveoparotitis" is only another manifestation of benign lymphogranulomatosis and that it is essentially the same disease as sarcoidosis, but with its most striking symptoms in the eyes and salivary glands rather than in the skin, lymph nodes and lungs. Longcope and Pierson stated that the histologic changes in the lymph nodes and parotid glands in cases of uveoparotid fever are almost precisely the same as in sarcoid, miliary epithelioid tubercles with occasional giant cells and with almost complete absence of necrosis or caseation. Garland and Thompson[6] recognized the same histopathology in this disease but considered the lesions to be tuberculous. They stated: "In one of Heerfordt's cases, a resected portion of the iris showed typical tuberculous lesions histologically—endothelial cells, lymphocytes, giant cells without caseation or tubercle bacilli. . . . In all cases in which biopsies have been performed, whether from the parotids or from the irides, the histologic features have been exactly similar, namely, an endothelial fibrosing tuberculosis in which caseation is absent and tubercle bacilli are not found." One of their patients, a woman, aged 28, with bilateral parotitis, bilateral iridocyclitis and uveitis and peripheral neuritis, showed at necropsy miliary tuberculosis involving the lungs, pericardium, myocardium, parotid and submaxillary glands, peritoneum, liver, kidneys and uterus.

Bruins Slot, Goedbloed and Goslings[3] reported a group of 6 cases of uveoparotitis and of Boeck's sarcoid in which there was a definite intermingling of symptoms in the individual cases. They gave as their opinion that the syndrome of Heerfordt is part of the syndrome of Besnier-Boeck. This opinion is supported, they think, by the histologic changes in the skin, lymph nodes, parotid glands and lacrimal glands. Walsh stated: "It seems unnecessary further to labor the point that uveoparotid fever and sarcoid are similar diseases and may be different manifestations of the same disease." King stated: "Parotid gland enlargement, which occasionally occurs in Boeck's sarcoid, was found in conjunction with uveal involvement in 2 of my cases. Uveoparotitis and Mikulicz's syndrome may both be manifestations of Boeck's sarcoid." With[24] stated that uveoparotid fever might be regarded as a special localization of benign lymphogranulomatosis. He advanced in support of this contention the following arguments: 1, the histology is the same—foci of epithelioid cells, few giant cells and little or no necrosis; 2, the bacteriology—prevailing inability to find tubercle bacilli in the tissues and to recover them by culture or by animal inoculation; 3, the glandular enlargements—which may involve any part of the body but are most frequent in the neck and at the hilus of the lungs; 4, infiltrations of the skin of the lupus pernio type have been seen in a number of cases of uveoparotid fever; 5, sarcoid may be limited to the salivary glands and the lacrimal glands with involvement of the uvea; and 6, tuberculin reactions are negative in a high percentage of cases. The greatest point of difference between sarcoidosis and uveoparotid fever lies in the frequency of involvement of the nervous system. Grönblad[7] is endeavoring to prove that Mikulicz's syndrome, uveoparotid fever and keratoconjunctivitis sicca (Sjögren) are all manifestations of sarcoidosis. Waldenström,[22] who mentioned that uveoparotitis may simulate encephalitis lethargica, stated that three characteristics, the tubercular structure without caseation, the large percentage of tuberculin negative cases, and the small number of cases in which tubercle bacilli are found in the lesions, immediately associate uveoparotid fever with another type of granuloma, the so-called morbus Besnier-Boeck." It must be regarded as highly probable that many cases of typical Mikulicz disease with fibrosis and round cell infiltration also represent late stages of the same anatomic process. Waldenström expressed the belief that this process, a universal benign tuberculoid granuloma, is the cause for a great variety of clinical pictures, Besnier-Boeck's disease, lupus pernio, many cases of Mikulicz disease, uveoparotid fever, and cases of so-called encephalitis lethargica with parotitis.

As has been stated previously in this review, there is a widespread, but as yet unwarranted, tendency among writers on sarcoid and on uveoparotid fever to regard both these diseases as unusual or benign forms of tuberculosis. So far, however, it has not been possible to prove definitely the tuberculous etiology of these lesions. Many of the arguments in favor of this view are based on the finding at necropsy of miliary tuberculosis in a patient who has presented earlier clinical evidence of sarcoidosis or uveoparotid fever. Horton, Lincoln and Pinner (quoted by King) report 4 cases of "non-caseating tuberculosis

(type: Boeck's sarcoid)," in 2 of which active uveitis was present and in 1 chorioretinitis and iridocyclitis. In 1 case at necropsy, caseating lesions of miliary tuberculosis were found and they, therefore, suggest that the sarcoids of Boeck represent a non-caseating phase of tuberculosis. A possible explanation for the absence of tubercle bacilli in these "non-caseating tubercles" is furnished by the studies of Kyrle (as noted by King). In experimental tuberculous lesions of the skin, Kyrle found that bacilli were abundant during the first 10 days after injection into the skin but had practically disappeared at the end of 5 weeks. At this time the typical histologic picture of sarcoid was present. Kyrle thinks, therefore, that sarcoid is a distinct type of foreign body reaction to tubercle bacilli and their disintegration products.

The evidence both for and against the tuberculous etiology of Boeck's sarcoid has been well summarized by King. It seems hardly necessary to repeat this evidence in detail in the present review. Those who are particularly interested in this phase of the subject can refer to his original article. Suffice it to say here that King is inclined to believe that the evidence against the tuberculous etiology is the more conclusive.

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PHYSIOLOGY.

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Roentgen-ray Diffraction Studies in Iodinated Amino Acids and Proteins. M. SPIEGEL-ADOLF, R. H. HAMILTON, JR., and G. C. HENNY (Department of Colloid Chemistry, D. J. McCarthy Founda-

tion, the Departments of Biochemistry and Physics, Temple University School of Medicine). In order to decide whether "the process of iodinating of the protein also changes the molecular configuration so as to produce physiologic activity" (Salter), Roentgen ray diffraction pictures by the powder method were taken from tyrosine, 3,5-di-iodo-tyrosine, 3,5-di-iodo-thyronine, thyroxine, thyroglobulin, casein, iodo-casein, and plastein derived from the latter substance. The Roentgen ray diffraction patterns show that the iodination of tyrosine and 3,5-di-iodo-thyronine brings forth noticeable changes in the diffraction patterns of the resulting substances 3,5-di-iodo-tyrosine and thyroxine. Two diffraction rings (corresponding to spacings of 4.36 and 5.03 A°) are strong in tyrosine and weak in the 3,5-di-iodo-tyrosine diffraction pattern. Conversely, at least two new diffraction rings, non-existing in tyrosine (corresponding spacings at 3.92 and 13 A°) become manifest in 3, 5-di-iodo-tyrosine and persist in di-iodo-thyronine and thyroxine. At least five of the 3,5-di-iodo-thyronine rings (corresponding spacings at 2.12, 2.37, 2.60, 3.04, 5.57 A°) are absent in thyroxine which alone shows a diffraction ring corresponding to a spacing of 3.62 A°. Effects of iodine presence can be detected neither in thyroglobulin nor in iodo-casein. The Roentgen ray diffraction pattern of plastein differs from that of the mother-substance in width of the side-chain and sharpness of the backbone reflection.

An Immunologic Investigation of the Mechanism of Glomerulonephritis. C. F. KAY, P. F. LUCCHESI, and R. B. RUTHERFORD (Department of Medicine, University of Pennsylvania and the Philadelphia Hospital for Contagious Diseases). A synopsis of past and present concepts of the mechanism by which acute glomerulonephritis develops was presented. The relation of certain types of experimental glomerulonephritis to these concepts was briefly discussed. Experiments were devised to determine whether patients with scarlet fever develop antibodies to human renal antigens or streptococcal toxin digests of renal tissue, or whether an unspecified circulatory antigen could be demonstrated to be present early in the disease by the development of specific antibodies at a later period. Complement fixation and precipitative methods were applied to the sera of 78 patients with scarlet fever. The results of these studies were completely negative. These experiments did not support the hypothesis that glomerulonephritis develops as a result of an antigen-antibody reaction. They pertained especially to the recent concept that the antigen concerned may be absorbed or combined with kidney cells or may be kidney cells themselves. Reasons are given why the results of this experiment cannot be taken to exclude the possibility of such a mechanism.

The Use of Sulfonamides in the Prevention of Experimental Brain Abscesses. G. M. MARKLEY (Harrison Department of Surgical Research, University of Pennsylvania). The purpose of this paper is to

report the results on the use of the sulfonamides in the prevention of the experimental brain abscess.

The technique for abscess production was the same as previously reported except the dose of the bacterial inoculum was increased.

The dose of sulfanilamide, sulfapyridine and sulfathiazole was 0.5 gm. per kilo daily in a single dose by mouth, and that of sulfadiazine was 0.25 gm. per kilo daily. All treated dogs received a course of 5 days of treatment. Determinations of blood concentrations of the various drugs were made daily before the administration of an additional dose. Control experiments were run simultaneously with treatment experiments.

Results: Sulfanilamide protected 66%, 100% and 75% of the dogs inoculated with pneumococcus Type III, *Staph. aureus* and *Strep. hemolyticus* respectively. Sulfathiazole protected 33%, 75% and 75% respectively. Sulfadiazine protected 100%, 75% and 50% respectively. Sulfapyridine protected 100% of the dogs inoculated with pneumococcus Type III when treatment began before 12 hours after inoculation and 75% of the dogs when treatment began 17 hours after inoculation. It protected only 20% of the dogs inoculated with streptococcus and was not used against *Staph. aureus*.

The mean blood concentration of the various drugs of the treated dogs which died was in every instance within the range of the mean blood concentration of the surviving dogs, except for those dogs receiving sulfadiazine. Even so these dogs maintained a mean blood concentration of 20.8 mg. per 100 cc. until the time of death.

Sulfadiazine proved least toxic in these experiments.

Conclusions: 1, Sulfonamide therapy is effectual in preventing pyogenic brain abscesses following injection of pneumococcus Type III, *Staph. aureus*, and *Strep. hemolyticus* into a cerebral area previously traumatized. 2, Sulfonamide therapy should be begun early. 3, Sulfanilamide and sulfadiazine were found to be the most effective compounds.

The Influence of Certain Commonly Used Drugs on the Rate of Gastric Emptying in the Normal Human Subject as Determined by an Intubation Technique. (Atropine, Morphine, Benzedrine, Prostigmine, Nitroglycerine, Syntropan, Mecholyl, Ergotamine Tartrate and Sodium Bicarbonate.) JARRETT H. FOLLEY and W. OSLER ABBOTT (Gastro-Intestinal Section, Hospital of the University of Pennsylvania). The gastric emptying time, as determined by roentgenoscopy under normal circumstances and as affected by drugs, has been frequently determined; but the gastric emptying rate has been more often guessed at than measured. After injecting 500 cc. of dilute milk into the stomach of normal adults it has been possible to quantitate the emptying rate by aspirating, measuring and reinjecting the gastric contents every 10 minutes until 90% of the initial volume has disappeared. Repeating this procedure 14 times on 5 subjects a total of 70 experiments has been performed, 15 of them controls, 55 exemplifying the effect of varying doses of atropine and of clinical doses of morphine, benzedrine,

prostigmine, nitroglycerine, "syntropan," "mecholyl," ergotamine tartrate and sodium bicarbonate. Although the expected side effects were noted assuring us of the potency of the drug, the results show no significant difference save after morphine when the emptying rate was slowed.

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